Clinical Neurosciences, Neurology
University of Helsinki

Stroke-induced excitability changes in human motor cortex

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ACADEMIC DISSERTATION
To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in Lecture Hall 3, Biomedicum Helsinki 1, Haartmaninkatu 8, Helsinki, on 23rd of March 2018 at 12 noon.

Helsinki, 2018

Academic dissertation

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ISBN 978-951-51-4076-0 (hardcopy)
ISBN 978-951-51-4077-7 (PDF)
http://ethesis.helsinki.fi
Unigrafia Oy
Helsinki 2018

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Acknowledgements

The work for this Thesis was carried out in the Brain Research Unit (BRU) of the O. V. Lounasmaa Laboratory and in the Department of Neuroscience and Biomedical Engineering (NBE), both of Aalto University, and in the Department of Neurology, Helsinki University Hospital (HUH). The MEG measurements were conducted in Aalto NeuroImaging MEG-Core, Aalto University, and in the Biomag Laboratory, HUH. The work was financially supported by Helsinki University Hospital Research Fund, SalWe Research Program for Mind and Body (Tekes; Finnish Funding Agency for Technology and Innovation) and Finnish Medical Foundation. Doctoral Program Brain & Mind has supported travels to conferences.

I wish to express my gratitude to Academician of Science, Professor Riitta Hari, the head of the former BRU, as well as to the head of NBE, Professor Risto Ilmoniemi, for their support and for providing me with all the facilities required for this research and for the opportunity to work in such an inspiring scientific atmosphere. I am grateful to my supervising Professor Timo Erkinjuntti, Department of Neurology, HUH, for his kind and supportive attitude towards my research. I also would like thank the former head of the Department of Neurology, Professor Markus Färkkilä for his positive stance towards my research.

I owe my deepest gratitude to my supervisor, the head of the Department of Neurology in HUH, docent Nina Forss for her support, guidance and patience throughout this work. Her broad knowledge of the sensorimotor system linked to her extensive experience in clinical neurology are admirable. She has the astonishing talent for multitasking and quick and fair decision making. I would also like to thank her for the several humorous chats concerning family life and health – the things that are the most important in life.

I wish to thank the preliminary examiners of my Thesis, Professor Pekka Jäkälä and Professor Esa Mervaala, for their valuable and insightful comments and suggestions that helped me to improve this Thesis. In addition, I want to thank Docent Tiina Sairanen and Docent Erika Haaksiluoto for their kind attitude and support as the members of my Thesis follow-up group.

My sincere thanks to all my co-authors, it has been a privilege to work with you. My deepest thanks to my husband and co-author, Professor Lauri Parkkonen for his partic-

ipation in this work. This Thesis could not have been carried out without your help in numerous problems concerning MEG-analysis and statistics. I want to thank you for your endless patience during these past years and numerous kitchen talks about brain research. I am deeply grateful to PhD Kristina Laaksonen for her invaluable help and profound concentration in this work. Her endless energy and enthusiasm towards this research are amazing. Her guidance and support throughout this work have been most helpful and encouraging. Furthermore, I want to thank her for all, and sometimes, profound conversations we have had. My sincere thanks to PhD Harri Piitulainen for his kindness and valuable help with the computation of the passive-movement kinematics. I wish to thank Docent Johanna Pekkola for her neuroradiological expertise, and Professor Turgut Tatlisumak for his participation in the planning of these studies and facilitating the recruitment of the patients.

My sincere thanks go to all the patients participating the measurements. Despite the serious illness, they were willing to engage in this research and help take science forward. I wish to thank also all the control subjects for providing me important reference data. I would like to warmly thank all the ergotherapists in HUH for performing the clinical testing of the patients.

My warmest thanks belong to laboratory assistant Mia Illman for her infinitely important help in all the MEG recordings and also for the support and precious friendship and fun leisure time together throughout this journey. I want to thank Docent Jyrki Mäkelä for supporting our MEG measurements in the Biomag Laboratory. I would like to thank all the other wonderful researchers with which I had the privilege to work over the years in the laboratory. Especially, my warm thanks to my roommate Siina Pamilo and dear colleagues Hanna Kaltiainen, Hanna Renvall and Jaakko Hotta with whom I have shared the delights and pains of research and life during these years.

I am deeply grateful to my former senior physician in Peijas Hospital, Docent Elena Haapaniemi and my current senior physician in Laakso Hospital, Päivi Paavola, for their flexibility and supportive attitude that have enabled me to complete this work. I wish to thank my colleagues in Laakso Hospital for sharing my shifts when I needed time for research and for the nice company at work and outside the hospital. I want to thank all my colleagues in the Department of Neurology in HUH for their support and nice, although busy, moments in the hospital and Emergency Unit. I owe my warmest thanks to all my friends outside the work for helping me relax during these years.

My dear mother Helvi and late father Pekka, thank you for your endless love and support in many ways throughout my life. Mom, thank you for those numerous telephone conversations and your supportive words when I had sorrows. My dear sister Leena and brothers Antti and Matti and your spouses Juha and Marjut and the children, I owe my gratitude for the nicest leisure time with you all; our gatherings have been the true rest for me. Thank you my dear parents-in-law Leena and Heikki and also Elina, Eero, Noora and Olavi for all your love and relaxing time together, especially in the nature and boating in the Finnish archipelago.

Finally, my deepest love and gratitude belong to my family. Lauri, thank you for supporting me through these years of our life together. You have always encouraged me in my decisions and stood by me during happy and hard times. Thank you for being so patient and endearing husband and father. My dear children Tapio and Aino, you are the joy and the reason in my life – I am so proud of you. Dear Julia, part of our family for many years, thank you for your delightful company. You all remind me what is the most important in life.

Espoo, February 2018
Eeva Parkkonen

Abstract

Despite advances in acute treatment of stroke, over third of the patients suffer from a disability, most often upper-limb paresis, still five years after stroke. To improve rehabilitation, further understanding of stroke-induced plasticity is required. During the plastic period, cortical excitability increases, likely promoting cortical reorganization.

Afferent input modulates the rolandic 20-Hz rhythm. The modulation, reflecting motor-cortex excitability, is observable as the activation-associated suppression and inhibition-associated rebound of the 20-Hz rhythm. In this Thesis, motor-cortex excitability was monitored by applying two different afferent inputs while recording the 20-Hz rhythm with magnetoencephalography (MEG), first in healthy controls and then in stroke patients in a one-year longitudinal study.

Study I, comprising 22 healthy controls, focused on the modulation of the 20-Hz rhythm to tactile stimulation and passive movement as proprioceptive stimulation. The suppression of the rhythm was similar to both stimuli whereas the rebound was stronger to passive movement. Thus, passive movement could better serve in studying motor-cortex excitability changes.

In Studies II and III, modulation of the 20-Hz rhythm to afferent input was measured in 23 patients having their first-ever stroke in the territory of the middle cerebral artery and related upper-limb paresis. Passive movement of the index finger (Study II) and tactile stimulation (Study III) were applied during MEG recordings in the acute (T_0; 1–7 days), subacute (T_1; one month) and chronic (T_2; 12 months) phases after stroke onset in conjunction with clinical testing of hand motor performance. The results showed that in the acute phase, the rebound was strongly diminished to both stimuli compared to the controls and increased significantly during the first month. During the follow-up period, the rebound strengths to both stimuli correlated with motor performance of the impaired hand.

The bilateral weakness of the rebounds in the acute phase indicate hyperexcitability of both hemispheres after stroke. The subsequent increase in the rebound strength during the first month, reflecting an increase in motor-cortex inhibition, is in line with earlier studies in animals and humans suggesting a sensitive and motor-recovery-related plastic period immediately after stroke. The rebound strength to impaired-hand stimulation correlated

with hand motor performance across the follow-up indicating that adequate integration of afferent input with motor functions is important for motor recovery. During the follow-up, the 20-Hz rebound to both tactile and passive-movement stimuli increased similarly. However, the rebounds to tactile stimuli recovered to the level of the controls whereas those to proprioceptive stimuli did not. This might indicate that proprioception did not recover fully in our patients.

It would be most important to be able to predict and evaluate the progress of an individual patient during recovery from stroke to intensify and tailor rehabilitation for individual needs. Though, the efficacy of rehabilitation may be evaluated with different neuroimaging methods and clinical tests in a group level, so far there are no objective biomarkers to evaluate rehabilitation in an individual level. The results of this Thesis indicate that the 20-Hz rebound magnitude strongly reflects motor-cortex excitability and thus could serve as a robust noninvasive marker of stroke-induced neurophysiological processes that are relevant for motor recovery. Such a biomarker may enable to assess the efficacy of new therapeutical methods in stroke rehabilitation in both group and individual levels.

Tiivistelmä

Aivoinfarktin akuuttihoidon kehittymisestä huolimatta yli kolmannes potilaista kärsii aivoinfarktin aiheuttamista vammoista, yleisimmin yläraajahalvauksesta, vielä viisi vuotta infarktin jälkeen. Kuntoutuksen tehostamiseksi aivoinfarktin jälkeistä aivojen muovautumiskykyä eli plastisiteettia tulisi ymmärtää nykyistä paremmin. Plastisen ajanjakson aikana aivokuoren aktivaatiotila on lisääntynyt, mikä todennäköisesti mahdollistaa aivokuoren uudelleenjärjestäytymisen.

Aistiärsykkeet moduloivat liikeaivokuoren rolandisen alueen 20 hertsin rytmiä. Rytmin modulaatio kuvastaa liikeaivokuoren aktivaatiotilaa, mikä voidaan havaita aktivaatioon liittyvänä rytmin vaimenemisena sekä inhibitioon liittyvänä rytmin elpymisenä ns. purskeena. Tässä väitöskirjatutkimuksessa liikeaivokuoren aktivaatiotilaa tutkittiin rekisteröimällä magnetoenkefalografiamenetelmällä (MEG) 20 hertsin rytmiä käyttäen kahta erilaista aistiärsykettä ensin terveillä verrokeilla ja sen jälkeen potilailla vuoden kestävässä pitkittäistutkimuksessa.

Osatutkimuksessa I mittasimme 20 hertsin rytmin muutoksia 22 terveellä verrokilla käyttäen kosketusärsykettä ja proprioseptisena ärsykkeenä passiiviliikettä. Rytmin vaimeneminen oli samankaltaista kummankin ärsykkeen vaikutuksesta, kun taas passiiviliike aiheutti voimakkaamman rytmin purskeen kuin kosketusärsyke. Siten passiiviliike voisi toimia paremmin tutkittaessa liikeaivokuoren aktivaatiotilan muutoksia.

Osatöissä II ja III mittasimme 20 hertsin rytmin modulaatiota 23 potilaalla, jotka olivat sairastuneet elämänsä ensimmäiseen aivoinfarktiin keskimmäisen aivovaltimon verisuonittamalla alueella ja siihen liittyen yläraajan halvaukseen. Aistiärsykkeinä käytimme etusormen passiiviliikettä (osatutkimus II) sekä kosketusärsykettä (osatutkimus III) MEG-mittauksen aikana akuutissa (1–7 päivää), subakuutissa (yksi kuukausi) ja kroonisessa (12 kuukautta) vaiheessa infarktiin sairastumisen jälkeen. Lisäksi kunkin mittauksen yhteydessä arvioitiin käden motorinen toiminta kliinisin testein. Tulokset osoittavat, että stimulaation jälkeinen rytmin purske oli akuutissa vaiheessa voimakkaasti heikentynyt molemmille ärsykkeille verrattuna verrokkien arvoihin, mutta ensimmäisen kuukauden aikana purske voimistui merkittävästi. Rytmin purskeen voimakkuus korreloi sairaan käden motorisen suorituksen kanssa koko seurantatutkimuksen ajan.

Rytmin purskeen heikkous akuuttivaihessa viittaa molempien aivopuoliskojen liikeai-

vokuorien hyperaktiivisuuteen. Purskeen voimistuminen ensimmäisen kuukauden aikana kuvastaa lisääntynyttä liikeaivokuoren inhibitiota, jota on havaittu aiemmissa aivoinfarktin jälkeistä herkkää ja lyhyttä sekä motoriseen toipumiseen liittyvää plastisiteettijaksoa osoittavissa eläin- ja ihmistutkimuksissa. Rytmin purskeen voimakkuus korreloi sairaan käden motorisen toiminnan parantumisen kanssa koko seurantajakson ajan viitaten siihen, että tuntoaistin ja proprioseptiivisen informaation integraatio motorisen aivokuoren toimintaan ovat tärkeitä motoriselle toipumiselle. Seurantajakson aikana 20 hertsin rytmi voimistui samankaltaisesti kummankin aistiärsykkeen, niin kosketusärsykkeen kuin proprioseptiivisen ärsykkeen vaikutuksesta. Purskeen voimakkuus kosketusärsykkeen vaikutuksesta kuitenkin saavutti terveiden verrokkien tason, kun taas proprioseptiiviselle ärsykkeelle se ei toipunut samalle tasolle kuin verrokeilla. Tämä saattaisi viitata siihen, että potilaidemme proprioseptiikka ei toipunut täysin.

Olisi tärkeää pystyä ennustamaan potilaan yksilöllistä toipumista aivoinfarktin jälkeen, jotta kuntoutusta voitaisiin tehostaa ja räätälöidä kunkin potilaan tarpeiden mukaan. Vaikka erilaisilla kuvantamistutkimuksilla ja kliinisillä mittareilla voidaankin arvioida kuntouksen edistymistä ryhmätasolla, toistaiseksi objektiivista yksilöllistä mittaria ei ole olemassa. Tämän väitöskirjatutkimuksen tulokset viittaavat siihen, että 20 hertsin rytmin purskeen suuruus kuvastaa voimakkaasti liikeaivokuoren aktiviteettimuutoksia ja voisi siten toimia luotettavana kajoamattomana mittarina tutkittaessa aivoinfarktin aiheuttamia ja motoriselle toipumiselle tarpeellisia liikeaivokuoren neurofysiologisisa muutoksia. Tällainen biomarkkeri mahdollistaisi uusien aivoinfarktin jälkeisten kuntoutusmenetelmien tehon arvioimisen sekä ryhmä- että yksilötasolla.

List of Publications

P1 **Parkkonen E**, Laaksonen K, Piitulainen H, Parkkonen L, Forss N (2015). Modulation of the ~20-Hz motor-cortex rhythm to passive movement and tactile stimulation. *Brain and Behavior* 5: 3–11.

P2 **Parkkonen E**, Laaksonen K, Piitulainen H, Pekkola J, Parkkonen L, Tatlisumak T, Forss N (2017). Strength of ~20-Hz Rebound and Motor Recovery after stroke. *Neurorehabilitation and Neural Repair* 5: 475–486.

P3 **Parkkonen E**, Laaksonen K, Parkkonen L, Forss N (2018). Recovery of the 20-Hz rhythm to tactile and proprioceptive stimulation after stroke. *Neural Plasticity* 2018: 7395798.

Author's contribution

Study I: I participated in the recruitment of the healthy subjects and performed half (11/22) of the MEG recordings in healthy controls with the aid of my co-authors. I analyzed the data and interpreted the results together with my co-authors. I was the principal author of the manuscript.

Study II: I participated in designing the experiments and recruited most of the patients (28/30) and performed their MEG recordings with the aid of my co-authors. I analyzed the data and interpreted the results together with my co-authors. I was the principal author of the manuscript.

Study III: I participated in designing the experiments and recruited most of the patients (28/30) and performed the MEG recordings with the aid of my co-authors. I analyzed the data and interpreted the results together with my co-authors. I was the principal author of the manuscript.

List of Abbreviations

AH	Affected hemisphere
AP	Action potential
BB	Box-and-Block test
BDNF	Brain-derived neurotrophic factor
BI	Barthel index
DTI	Diffusion tensor imaging
EEG	Electroencephalography
FFT	Fast Fourier transform
fMRI	Functional magnetic resonance imaging
GABA	Gamma-Aminobutyric acid
HUH	Helsinki University Hospital
ICH	Intracerebral hemorrhage
ICI	Intracortical inhibition
ISI	Interstimulus interval
MCA	Medial cerebral artery
MEG	Magnetoencephalography
MEP	Motor evoked potential
MNE	Minimum-norm estimation
MRI	Magnetic resonance imaging
MI	Primary motor cortex
NIHSS	National Institutes of Health Stroke Scale
PEG	Nine-hole peg board test
PET	Positron emission tomography
PPC	Posterior parietal cortex
PSP	Post-synaptic potential
QEEG	Quantitative electroencephalography
rTMS	Repetitive transcranial magnetic stimulation
SAH	Subarachnoid hemorrhage
SEF	Somatosensory evoked field
SMA	Supplementary motor area
SQUID	Superconducting quantum interference device
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex

tDCS	Transcranial direct current stimulation
TFR	Time–frequency representation
TMS	Transcranial magnetic stimulation
TSE	Temporal spectral evolution
tSSS	Temporal signal-space separation
UH	Unaffected hemisphere
VPL	Ventral posterior lateral nucleus

1 Introduction

Stroke causes human suffering and is a huge economical burden for the society. Primary and secondary stroke prevention are therefore extremely important. Globally, stroke is the second-leading cause of death after heart diseases (Benjamin *et al.*, 2017) and it is a major cause of disability (Luengo-Fernandez *et al.*, 2013; Mozaffarian *et al.*, 2015).

Stroke induces plasticity, resembling the developing brain. Plasticity is based on the brain's capability to undergo molecular, structural and neurophysiological changes and it enables recovery leading to amelioration of motor deficits caused by stroke (Murphy and Corbett, 2009; Zeiler *et al.*, 2013). Animal studies have shown that within the plastic period, molecular (Jones *et al.*, 1996; Brown *et al.*, 2009; Wang *et al.*, 2011, 2012; Cramer and Chopp, 2000; Jin *et al.*, 2006; Carmichael *et al.*, 2001; Carmichael, 2003; Carmichael *et al.*, 2005; Carmichael, 2006) and structural changes such as reorganization of the motor cortex (Nudo and Milliken, 1996; Nudo *et al.*, 1996; Jones and Schallert, 1992; Schiene *et al.*, 1996; Xerri *et al.*, 1998) take place. Stroke-induced reorganization, i.e. enlargement of sensorimotor cortical areas, has been observed also in humans (Bütefisch *et al.*, 2003, 2005; Ward *et al.*, 2003b,a; Weiller *et al.*, 1992, 1993; Liepert *et al.*, 1998, 2000, 2005; Cramer and Crafton, 2006; Rossini *et al.*, 1998b). Plasticity-associated changes in motor-cortex excitability, enabling cortical reorganization, have been observed in several animal (Biernaskie *et al.*, 2004; Murphy and Corbett, 2009; Jablonka *et al.*, 2010) and human studies (Liepert *et al.*, 1998, 2000, 2005; Manganotti *et al.*, 2008; Bütefisch *et al.*, 2003, 2005; Swayne *et al.*, 2008; Di Lazzaro *et al.*, 2010, 2012; Weiller *et al.*, 1993; Nelles *et al.*, 1999; Cramer *et al.*, 1997; Tecchio *et al.*, 2005, 2006; Laaksonen *et al.*, 2012).

Understanding the pathophysiology of stroke is essential to improve rehabilitation. The aim of this Thesis was to elucidate stroke-induced acute and long-term neurophysiological changes in the motor cortex. Alterations in motor-cortex excitability, reflected in the modulation of the 20-Hz rhythm, were studied with magnetoencephalography (MEG) by using tactile and proprioceptive stimuli during a one-year follow-up. The goal was to clarify the temporal behavior of motor-cortex excitability changes after stroke and thereafter to correlate the rebound strength with hand motor performance to find a robust tool to monitor individual recovery of a patient after stroke and to evaluate the efficacy and safety of novel therapeutical methods targeting to enhance plasticity.

2 Background

2.1 Somatosensory system

2.1.1 Somatosensation and somatosensory pathways

The somatosensory system comprises four major modalities: discriminative touch, proprioception, nociception and pain. In this Thesis, we used tactile and proprioceptive stimuli during MEG recordings. The following sections focus on tactile sense and proprioception.

Tactile mechanoreceptors in the superficial skin and in subcutanic space respond to mechanical stimulation. Mechanoreceptors vary in receptive-field sizes and adaptation rates. The receptor capsules are innervated by peripheral axons of nerve cells in dorsal root ganglia. Proprioceptors, responsible for monitoring body position and movement, are located mainly in muscle spindles but also in tendons and joints. The sensory afferents, half of them primary and the other half secondary, ascend ipsilaterally along the spinal cord to the dorsal cuneate nucleus. In the medulla, the afferents synapse with the second- or third-order neurons, decussate and project to the thalamus as a fibre bundle called medial lemniscus, which in turn projects to the ventral posterior lateral nucleus (VPL) of the thalamus. From VPL the afferent pathways run through the internal capsule to the primary somatosensory cortex (SI) and to the secondary somatosensory cortex (SII; Kandel *et al.*, 1991).

2.1.2 Somatosensory cortex and its connections

Tactile afferents project from the thalamus to the SI located in the postcentral gyrus. Brodmann area 3b in the SI receives the main proportion of tactile information. Neurons in 3b project to areas 1 and 2 in the SI. Tactile input is further processed in the secondary somatosensory cortex (SII) and in the posterior parietal cortex (PPC), and then conveyed through cortico–cortical connections e.g. to the primary motor cortex (MI; Jones and Wise, 1977; Jones *et al.*, 1978; Jones, 1983). Only sparse or none direct connections from area 3b to the MI exist (Asanuma *et al.*, 1979). In addition, there are also direct projections from the thalamus to areas 1 and 2 and to the MI (Asanuma *et al.*, 1979; Goldring and Ratcheson, 1972; Lucier *et al.*, 1975; Naito *et al.*, 1999; Naito and Ehrsson, 2001).

The SII cortex receives input from all SI areas (Jones *et al.*, 1978). Furthermore, the SII has connections to the PPC (area 7), to the insular cortex and to the contralateral SII through transcallosal connections (Burton, 1986). In addition, the ipsilateral SII probably receives direct thalamocortical connections (Rowe *et al.*, 1996), at least if the SI activation is disrupted due to e.g. stroke (Forss *et al.*, 1999). Proprioceptive input from muscles is mainly conveyed to area 3a of the SI cortex, which projects to area 2 of the SI, to the SII, PPC, MI and supplementary motor area (SMA) (Jones, 1983; Kaas, 1993; Shibasaki *et al.*, 1980; Lee *et al.*, 1986; Chen *et al.*, 1999; Alary *et al.*, 1998, 2002; Disbrow *et al.*, 2000; Lange *et al.*, 2001; Druschky *et al.*, 2003; Hinkley *et al.*, 2007).

The SI cortex is somatotopically organized. The body areas where tactile discrimination is most important, such as the tongue and finger tips, have the largest representation areas reflecting their extensive innervation. According to the somatomotor homunculus, the representation areas for legs lie most medially, followed by the trunk, arms and most laterally the hand and face areas (Kandel *et al.*, 1991). Transcallosal connections between the SI cortices exist predominantly between areas 2, but to some extent also from areas 1 and 3b (Killackey *et al.*, 1983). In addition, SI projects to the contralateral SII (Burton, 1986).

2.2 Motor system

2.2.1 Motor cortex and its connections

The primary motor cortex (MI; Brodmann area 4) controls voluntary body movements. It sends motor commands, together with other motor areas, to spinal motoneurons in the corticospinal tract. The MI occupies the cortical area lying anterior to the central sulcus in the precentral gyrus and fissure in the frontal lobe. The MI follows the somatotopic organization of the SI; the face area lies most laterally and the lower limb area most medially. Premotor areas (Brodmann area 6), are also organized similarly and divided into two parts; the supplementary motor area (SMA) is located anteromedially to the MI and the premotor cortex is situated laterally. Stimulation of the premotor cortex typically evokes coordinated contractions of muscles at more than one joint, and stimulation of the SMA elicits contractions on both sides of the body (Kandel *et al.*, 1991). In the MI cortex, layer 5 contains the large pyramidal cells; the motor-cortical signals measured in MEG and EEG are generated in the apical dendrites of these pyramidal cells.

The primary motor cortex receives input from the periphery directly via the ventral posterior lateral nucleus of the thalamus and indirectly from the SI and SII. The premotor areas are connected with the sensory association areas. In addition, the motor areas receive input from the cerebellum and basal ganglia via the thalamus, mostly to the MI and to the premotor cortex. Intracortical connections exist between the MI and SMA, which, in turn, are influenced by input from the PPC and prefrontal association cortices (Kandel *et al.*, 1991).

2.2.2 Motor pathways

The corticospinal tract comprises axons from cortical layer 5; half of them originate in the MI and the rest mainly in the SMA and to a lesser extent also in the premotor cortex and the SI (areas 1, 2 and 3). The corticospinal tract terminates in the intermediate and ventral zones of the spinal cord. The corticospinal neurons form direct excitatory polysynaptic contacts with alpha motoneurons. In addition, corticospinal neurons connect with propriospinal neurons in the upper cervical segments of the spinal cord and thus influence indirectly alpha motoneurons. Furthermore, connections via interneurons mediate corticospinal inhibition to alpha motoneurons. The corticospinal tract is the only pathway controlling distal muscles of fingers. Feedback loops outside the corticospinal tract exist between all cortical motor areas, the basal ganglia and the cerebellum. These connections are polysynaptic and control complex movement patterns and learning of movements (Kandel *et al.*, 1991).

2.3 Brain rhythms

The mammalian brain generates several distinct neurophysiological rhythms. These spontaneous brain oscillations, produced by large populations of synchronized neurons, can be characterized by their frequencies and generation areas. Neurophysiological functions in certain cortical regions can be studied by exploring the dynamics of the corresponding rhythm. For example, the rolandic rhythms react to sensory stimuli and motor tasks.

2.3.1 Mu rhythm

Oscillations around 10–30 Hz are observed over the primary somatosensory and motor areas, also referred to as rolandic cortex. They were first detected with intracranial recordings by Jasper and Penfield (1949) and named as mu rhythm by Gastaut in 1952 (Hari and Puce, 2017). This rhythm has at least two distinct frequency components; one around 10 Hz and another around 20 Hz. The 10-Hz component appears to be generated more posteriorly in the postcentral gyrus (SI) and the 20-Hz component, also called beta rhythm, more anteriorly in MI, in the precentral gyrus (Salmelin and Hari, 1994; Salmelin *et al.*, 1995a; Pfurtscheller *et al.*, 1996).

It has been suggested that there are at least two distinct beta components according to their functions and frequencies; the lower component around 15 Hz and the higher one around 20 Hz (Pfurtscheller *et al.*, 1997; Jurkiewicz *et al.*, 2006; Hall *et al.*, 2011). These distinct components respond differently to movement; the 15-Hz beta is more associated to movement-cessation-related rebound and the 20-Hz beta is believed to react to the stimulus similarly than the 10-Hz component of the mu rhythm (Pfurtscheller *et al.*, 1997).

The beta rhythm is suppressed (event-related desynchronisation, ERD) by voluntary movement (Gastaut, 1952; Salmelin and Hari, 1994), by passive movement (Chatrian *et al.*, 1959; Alegre *et al.*, 2002), by electrical median nerve stimulation (Salmelin and Hari, 1994; Salenius *et al.*, 1997), and by tactile stimulation (Chatrian *et al.*, 1959; Cheyne, 2013). Furthermore, movement observation (Hari *et al.*, 1998) and motor imagery (Schnitzler *et al.*, 1997) have been shown to suppress the beta rhythm. After 0.5–2.5 s of movement or stimulus cessation, the amplitude of the rhythm transiently increases as a rebound (event-related synchronization, ERS). It has been suggested that the rebound is generated in the anterior side of the central sulcus and the suppression in post-central cortical areas (Salmelin *et al.*, 1995a,b; Pfurtscheller *et al.*, 1996; Jurkiewicz *et al.*, 2006).

Afferent input affects motor functions by modulating the excitability of the motor cortex (Abbruzzese *et al.*, 1981; Asanuma and Arissian, 1984; Favorov *et al.*, 1988; Cassim *et al.*, 2000, 2001). The 20-Hz rhythm is bilaterally modulated to unilateral stimulation, however, the reactivity in the hemisphere ipsilateral to the stimulated hand is weaker and less consistent compared to that in the contralateral hemisphere (Salenius *et al.*, 1997; Salmelin and Hari, 1994). In EEG and MEG studies, the suppression of the 20-Hz rhythm is suggested to reflect an active state of the MI, whereas the rebound, associated to the

termination of the movement or stimulus, is believed to represent a deactivated, or inhibited, state of the MI (Pfurtscheller *et al.*, 1996, 1997; Cassim *et al.*, 2000; Neuper and Pfurtscheller, 2001; Takemi *et al.*, 2013). Furthermore, in transcranial magnetic stimulation (TMS) studies, motor-cortex excitability has been shown to be decreased after cutaneous and median-nerve stimulation at the same latencies as the 20-Hz rebound occurs (Chen *et al.*, 1999; Abbruzzese *et al.*, 1981). In line, a combined MEG and magnetic resonance spectroscopy study has been shown a positive correlation of the 20-Hz rebound strength with the concentration of gamma-amonibutyric acid (GABA), which acts as an inhibitory neurotransmitter (Gaetz *et al.*, 2011).

The 20-Hz rebound has been shown to increase as a function of time from childhood, over adolescence to adulthood, reflecting reduced motor-cortical inhibition during early development (Gaetz *et al.*, 2010). Moreover, the rebound has been shown to be attenuated in disorders with suspected motor-cortex hyperexcitability, such as in Unverricht–Lundborg type epilepsy or complex regional pain syndrome (Juottonen *et al.*, 2002; Silén *et al.*, 2000; Visani *et al.*, 2006; Kirveskari *et al.*, 2010).

2.3.2 Other brain rhythms

The alpha rhythm was first measured by Hans Berger in 1929. The rhythm is generated in the thalamus and multiple cerebral cortical areas, prominently in the parieto-occipital cortex. This oscillation of 8–13 Hz is suppressed when eyes are open and increases while eyes are closed. The alpha rhythm is related to synchronization of cortical and thalamic activity (Steriade *et al.*, 1990). Modulation of the alpha band has been associated to gating of sensory input (Jensen and Mazaheri, 2010; Buchholz *et al.*, 2014).

Delta oscillations (< 3.5 Hz) occur in healthy adults only during sleep, and they are a sign of a pathological condition if present when the person is awake. The theta rhythm, oscillating between 4–7.5 Hz, may occur during sleepiness and in pathological brain conditions. However, it is also related to memory and functioning of the hippocampus. The gamma rhythm (> 40 Hz, even up to 600 Hz) consist of differently functioning subfrequencies. Increased gamma activity is linked with perceptual and cognitive tasks, such as sensorimotor coordination, multitasking and memory (Hari and Puce, 2017).

2.4 Stroke

2.4.1 Epidemiology

"A stroke is a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal (and at times global) disturbance of cerebral function, with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin" (Hatano, 1976). Although age-standardized rates of stroke mortality have decreased globally during the past two decades, the absolute number of patients having stroke every year, living with the consequences of stroke and dying from stroke, is increasing (Feigin *et al.*, 2017). In 2013, there were almost 26 million stroke survivors globally.

Approximately 70–80% of stroke patients suffer from an ischemic stroke, 10–15% from intracerebral hemorrhage (ICH), 5% from subarachnoid hemorrhage (SAH) and the rest from other types of stroke (Feigin *et al.*, 2017). In an ischemic stroke, a thrombosis in a cerebral artery prevents blood flow in a particular brain area, leading to a number of clinical symptoms, of which hemiparesis – particularly of the upper limbs – is the most common (Dobkin, 1991; Lawrence *et al.*, 2001). Strokes in the territory of the medial cerebral artery (MCA) result to upper limb paresis in 80% of the cases (Lawrence *et al.*, 2001) and may be accompanied with a number of other symptoms such as lower limb paresis, loss of sensation in the contralesional limbs and difficulties in the production or comprehension of speech.

The risk factors for stroke include modifiable behavioral factors (smoking, poor diet, low physical activity), metabolic risk factors (hypertension, obesity, diabetes and hypercholesterolemia) and environmental ones such as air pollution and lead exposure (Feigin *et al.*, 2016). Successful control of behavioral and metabolic risk factors would avert more than three quarters of the global burden of stroke. Data from a cohort of four U.S. communities followed from 1987 through 2013 showed that the major risk factors for stroke are decreasing, more in whites than in blacks (Nadruz *et al.*, 2017). On the other hand, increasing obesity and physical inactivity increase stroke in young adults (Kernan and Dearborn, 2015).

2.4.2 Treatment of stroke: ”Time is Brain”

The effective medical treatment in acute stroke is time dependent; thrombolysis with a human recombinant tissue plasminogen activator (rt-PA) in selected patients reduce brain damage and improve the outcome when administered intravenously within 3–4.5 hours or intra-arterially in 3–6 hours from the onset of symptoms (Hacke *et al.*, 2004, 2008; Lees *et al.*, 2010; Schellinger *et al.*, 2004). The benefit of endovascular treatment is the greater the earlier it is initiated, irrespective of age or stroke severity (Emberson *et al.*, 2014; Kennedy *et al.*, 2016). Revascularization achieved by mechanically removing a clot by intra-arterial thrombectomy has considerably increased the success of acute stroke therapy (Wartenberg and Mayer, 2017). However, the treatment of acute stroke is effective only within a limited time window. According to the Brain Attack Coalition, the time from arrival at the emergency room to the initiation of thrombolysis should be 60 min or less (Alberts, 2017). Yet, the most significant delay, and hence the most important factor deteriorating the outcome, is during the pre-hospital phase; a patient-related delay in recognizing the symptoms and calling for help. Future developments of acute stroke treatment should focus on improving the procedures at all steps, starting from symptom onset, and especially shortening the pre-hospital time. In Helsinki University Hospital (HUH), the door-to-needle time of administering thrombolysis has been markedly reduced in recent years (Meretoja *et al.*, 2012), and nowadays the treatment can be offered within 17–18 min of patient arrival. However, several reasons, such as anticoagulant use, high blood pressure, recent surgery or hemorrhage and current cancer may exclude the patient from thrombolysis treatment.

Despite the advances in treatment, most of the patients do not reach effective acute treatment in time or they do not fully benefit from it. Globally, stroke is a leading cause of disability causing impairment in movement and sensation (Donnan *et al.*, 2008; Lloyd-Jones *et al.*, 2009). Most of the stroke survivors remain permanently disabled (Mozaffarian *et al.*, 2015).

2.4.3 Stroke-induced plasticity

Several studies in rodents have suggested that the early post-stroke period represents a phase of increased brain plasticity (Wang *et al.*, 2011; Biernaskie and Corbett, 2001; Biernaskie *et al.*, 2004; Murphy and Corbett, 2009; Brown *et al.*, 2009; Jablonka *et al.*, 2010). These plastic changes have been shown in humans as well (Duncan *et al.*, 1992;

Liepert *et al.*, 2000; Bütefisch *et al.*, 2003, 2005; Prabhakaran *et al.*, 2008; Swayne *et al.*, 2008). Stroke induces spontaneous, molecular, neurophysiological and structural changes enabling neurological improvement.

Molecular and structural changes

In adult rat brain, an ischemic injury results to changes in gene expression and increases levels of proteins which normally are associated with early stages of development, leading to elevated metabolism in the peri-infarct zone but also in the unaffected hemisphere (Cramer and Chopp, 2000). These proteins influence the extracellular matrix, glial structure, neuronal growth, cell apoptosis, angiogenesis and cellular differentiation. In addition, structural changes, such as lesion-induced dendritic arborization and synaptogenesis, have been found in adult rats after unilateral lesions in the sensorimotor cortex (Jones *et al.*, 1996). Furthermore, there is evidence that neurons can promote intrinsic factors, such as brain-derived neurotrophic factor (BDNF), for axonal regeneration (Comelli *et al.*, 1992; Chen and Zheng, 2014). In addition, expression of growth-inhibitory proteins are shown to be diminished, leading to axonal sprouting (Carmichael *et al.*, 2001, 2005; Carmichael, 2006).

Neurophysiological changes

Stroke-induced changes in motor-cortex excitability in both hemispheres have been documented in several studies. Hyperexcitation (disinhibition) of the motor cortex has been shown in animals acutely after stroke (Domann *et al.*, 1993; Buchkremer-Ratzmann *et al.*, 1996; Schiene *et al.*, 1996, 1999; Hagemann *et al.*, 1998; Jaenisch *et al.*, 2016). Similarly in humans, non-invasive neurophysiological methods and functional imaging have revealed hyperexcitation both in the affected and unaffected hemispheres in the acute phase after stroke (Liepert *et al.*, 2000, 2004; Manganotti *et al.*, 2002, 2008; Bütefisch *et al.*, 2003, 2005; Swayne *et al.*, 2008; Di Lazzaro *et al.*, 2010, 2012; Weiller *et al.*, 1993; Nelles *et al.*, 1999; Cramer *et al.*, 1997; Tecchio *et al.*, 2006; Laaksonen *et al.*, 2012). Decreased GABAergic inhibition in the affected hemisphere of rats in the acute phase of focal cortical strokes induced long-term potentiation (LTP), which is crucial for plasticity and learning (Hagemann *et al.*, 1998). Thus, hyperexcitability of the motor cortex likely leads to functional reorganization of motor cortical areas and restoration of motor functions (Liepert *et al.*, 2000; Bütefisch *et al.*, 2003, 2005; Nudo and Milliken, 1996; Nudo *et al.*, 1996; Ward *et al.*, 2003a; Ward and Frackowiak, 2003). Conflicting

results have also been reported by proposing that in the acute phase of stroke, increased GABA-mediated tonic inhibition would be important in functional recovery, probably by protecting the brain from toxic glutamergic effects (Clarkson *et al.*, 2010).

Studies in rats have suggested that after the acute hyperexcited phase, increased GABA-mediated intracortical inhibition (ICI) is necessary for improved motor function (Calautti *et al.*, 2001; Schiene *et al.*, 1996; Jaenisch *et al.*, 2016). A consistent decrease in motor-cortex excitability and the return of enlarged cortical representation areas to their initial sizes are shown to be a prerequisite for succesful motor recovery (Ward and Frackowiak, 2003; Cramer and Crafton, 2006; Buchkremer-Ratzmann and Witte, 1997; Roiha *et al.*, 2011; Rehme *et al.*, 2012). Prolonged hyperexcitability of the affected and unaffected hemispheres is suggested to hamper motor recovery (Liepert *et al.*, 2000, 2004, 2005; Manganotti *et al.*, 2002, 2008; Jaenisch *et al.*, 2016) and bilaterally increased inhibition is associated with good motor recovery (Calautti *et al.*, 2001; Tecchio *et al.*, 2006; Swayne *et al.*, 2008; Di Lazzaro *et al.*, 2012; Laaksonen *et al.*, 2012).

2.4.4 Predicting recovery from stroke

There have been several attempts to predict motor recovery after stroke. Severe impairments in motor and sensory functions in the acute phase are associated with poor functional outcome in the long run (Broeks *et al.*, 1999; Duncan *et al.*, 1992; Kwakkel *et al.*, 2003; Meldrum *et al.*, 2004). In stroke patients, motor impairment is commonly measured with the Fugl–Meyer scale, which assesses motor functioning, balance, sensation and joint functioning (Fugl-Meyer *et al.*, 1975). Excluding most seriously injured individuals, impairment in the acute phase is shown to be a reliable predictor of recovery; according to the proportional recovery rule, patients achieve recovery of around 70% of their initial recovery potential (difference of acute values vs. age- and gender-matched normative values) within six months (Prabhakaran *et al.*, 2008). This rule has been verified by other studies (Zarahn *et al.*, 2011; Winters *et al.*, 2015).

Brain connectivity -based methods have shown predictive value. Patients with upper-limb paresis followed the proportional recovery rule if they had a greater initial integrity of the corticospinal tract, measured by combining TMS with diffusion-weighted MRI (Byblow *et al.*, 2015) and by using diffusion tensor imaging (DTI; Guggisberg *et al.*, 2017). Congruently, a DTI study has indicated that the integrity of corticospinal tracts and transcallosal MI–MI connections in patients with severe chronic strokes are associated

with a good hand motor outcome (Lindenberg *et al.*, 2012). A recent TMS-study showed that patients with a severe hemiparesis and disruption of the corticospinal tract recovered poorly (Stinear *et al.*, 2017). The volume of interhemispheric tracts between the MI cortices has been shown to predict both short- and long-term motor outcome measured with the Box-and-Block test (Lindow *et al.*, 2016). EEG recordings have shown that the stronger the coherence in the 13–20-Hz band of language and motor areas with other brain regions the better the language and motor performance of the patients at 2–3 weeks and at three months post-stroke. In other words, the stronger the functional connectivity in the early post-stroke phase the better the language and motor functions recover (Nicolo *et al.*, 2015).

Studies investigating neuronal excitability changes after stroke may offer an interesting possibility to monitor and even predict recovery. The early hyperexcitation of both hemispheres is associated to the improvement of motor functions (Liepert *et al.*, 2000; Bütefisch *et al.*, 2003, 2005). However, the following shift of the affected hemisphere to reduced excitability has been associated with better recovery with positron emission topography (Calautti *et al.*, 2001), with TMS (Manganotti *et al.*, 2002) and with MEG (Laaksonen *et al.*, 2012).

Good motor recovery is related to a gradual decrease of the hyperactivation of relevant brain areas (Ward *et al.*, 2003b). Along these lines, enlargement of the hand area in SI in the acute phase after stroke and the subsequent normalization of this area have been linked to good hand motor recovery (Roiha *et al.*, 2011). In general, the return of the activation to the original level and decreased excitability in the unaffected hemisphere are associated to better functional recovery (Rehme *et al.*, 2012).

Poor motor outcome has been shown in stroke patients with a shift of interhemispheric balance towards the unaffected hemisphere (Cramer and Crafton, 2006) or with a constant engagement of areas distant from the lesion. A cross-sectional fMRI study in stroke patients showed that the more regions (in addition to MI, SMA, cingulate motor areas, PPC and cerebellum) in both hemispheres were activated to a motor task at three months after stroke the worse was the recovery (Ward *et al.*, 2003a). Accordingly, combined MEG and fMRI studies showed a persisting enlargement of the hand representation areas in MI in both hemispheres (Rossini *et al.*, 1998b) and a posterior relocation of the sensorimotor areas (Rossini *et al.*, 1998b,a) in patients with poor motor recovery. However, in a severe stroke, hyperexcitation of the more distant cortical areas may provide at least some degree of regained motor function.

A meta-analysis of TMS studies in 472 stroke patients has shown that increased activation in the ipsilesional MI, pre-SMA, contralesional premotor cortex and cerebellum is associated with better hand motor outcome, however, recruitment of the original functional connections is associated to good functional recovery (Rehme *et al.*, 2012). A meta-analysis comprising 112 TMS studies suggests that the neurophysiological effects of stroke mainly occur in the affected hemisphere, and that there is no explicit evidence of increased excitability in the unaffected hemisphere or imbalanced interhemispheric inhibition (McDonnell and Stinear, 2017). Nevertheless, a quantitative electroencephalographic method (QEEG) has indicated that interhemispheric voltage asymmetry predicts a poor outcome measured with NIHSS (Finnigan and van Putten, 2013). In addition, another QEEG study has shown a positive correlation of a decrease in delta-band activity with NIHSS scores at 30 days after stroke (Finnigan *et al.*, 2004). A systematic review of the data from 14 TMS studies suggests that motor-evoked potentials (MEPs) elicited over the M1 in the acute and subacute phases after stroke could predict functional recovery; however, due to methodological differences in these studies the prognostic value should be proved in larger prospective studies (Bembenek *et al.*, 2012).

The studies aiming to monitor and predict motor recovery from stroke are mainly focusing to group level rather than to individual recovery. However, in an earlier MEG study, the modulation of the 20-Hz rhythm to tactile stimulation was studied in moderately injured stroke patients in the acute phase, one and three months after stroke. The results showed that the strongest increase in the rebound strength was observed during the first month after stroke indicating decreased motor-cortex excitability. Furthermore, the 20-Hz rebound strength correlated with hand motor performance measured with NHPT at all time points. (Laaksonen *et al.*, 2012).

Stroke patients with mild or moderate neurological deficits follow the proportional recovery rule, i.e., their outcome shows a clear relationship to their initial impairment (Prabhakaran *et al.*, 2008). Only about half of the patients with severe neurological deficits (facial palsy, severe lower-limb paresis and absence of finger extension) within 72 hours after stroke follow the rule. It is still somewhat obscure why some patients with severe stroke show less impairment (Prabhakaran *et al.*, 2008; Winters *et al.*, 2015). Hence, there is a clear need to find objective, clinically-applicable biomarkers, which could be used to predict and evaluate recovery during rehabilitation, especially in a severe stroke.

2.4.5 Stroke rehabilitation

Intensive training

Several studies have indicated that the most effective plastic changes occur shortly after stroke, mainly during the first month in rodents (Biernaskie *et al.*, 2004; Jablonka *et al.*, 2010; Krakauer *et al.*, 2012; Murphy and Corbett, 2009) and up to a maximum of three months in humans (Prabhakaran *et al.*, 2008; Duncan *et al.*, 1992; Krakauer *et al.*, 2012; Forss *et al.*, 2012; Laaksonen *et al.*, 2012). This time-limited plastic period includes spontaneous biological recovery, which is suggested to follow the proportional recovery rule despite the given rehabilitation form (Prabhakaran *et al.*, 2008). However, only about half of the patients with a severe stroke follow this rule (Prabhakaran *et al.*, 2008; Winters *et al.*, 2015). Hence, there might be factors, which are not associated with initial spontaneous recovery, and thereby, they could be enhanced by intensive rehabilitation (Ward, 2017).

Early (within one week from stroke onset), organized and intensive, multiprofessional rehabilitation has been shown to influence patient's long-term outcome (Musicco *et al.*, 2003; Stroke Unit Trialists' Collaboration, 2007; Peurala *et al.*, 2014). Several animal and human studies support the idea that the timing of post-stroke training is essential for better motor recovery; rehabilitative training during the plastic period probably influences neuronal inhibitory circuits in the preserved surrounding sensorimotor cortex resulting to reorganization of cortical ares and recovery of motor functions after stroke (Nudo and Milliken, 1996; Biernaskie and Corbett, 2001; Biernaskie *et al.*, 2004; Barbay *et al.*, 2006; Forss *et al.*, 2012; Kleim and Jones, 2008; Lohse *et al.*, 2014; Murphy and Corbett, 2009; Brown *et al.*, 2009; Wang *et al.*, 2011). Amelioration of motor functions beyond the plastic period is probably mediated mainly by compensation (Zeiler *et al.*, 2013).

Enrichment of the environment and physical activity after stroke have shown to result to favorable outcomes after focal ischemia in rats (Ohlsson and Johansson, 1995; Johansson and Ohlsson, 1996). Also intensive motor-task training after focal ischemia in primates have indicated to be beneficial for motor outcome (Nudo and Milliken, 1996). In clinical studies in humans, restraining the use of a healthy limb and enhanced training with the impaired limb (constraint-induced therapy) after stroke have shown to be effective for motor recovery (Taub *et al.*, 1993; Liepert *et al.*, 2000). Furthermore, enrichment of the environment in conjunction with intensive task-specific training after stroke is suggested to profoundly improve functional outcome (Biernaskie and Corbett, 2001).

Non-invasive neural stimulation

Utilization of peripheral or central nerve stimulation aims to produce afferent feedback or affect motor-cortex excitability. Functional electrical stimulation (FES) applied to hemiparetic upper limb muscles likely stimulates proprioceptive sensory afferents and may have a moderate effect on motor recovery after stroke (Hara, 2008; Howlett *et al.*, 2015). Ongoing trials may show whether a painless repetitive peripheral magnetic stimulation (rPMS) improves motor function after stroke (Momosaki *et al.*, 06 23, 2017).

As stroke induces alterations in motor-cortex excitability, rehabilitative interventions influencing motor-cortical excitatory–inhibitory circuits offer a promising approach to augment post-stroke motor recovery. Increased excitability in the affected hemisphere in the acute phase after stroke is suggested to lead to long-term potentiation (Hagemann *et al.*, 1998) and enlargement and re-organization of cortical representation areas (Schiene *et al.*, 1999; Liepert *et al.*, 2000; Bütefisch *et al.*, 2003; Ward *et al.*, 2003a; Ward and Frackowiak, 2003; Cramer and Crafton, 2006).

Non-invasive brain stimulation techniques, such as repetitive TMS (rTMS) with a high-frequency pulse train over the motor cortex, are suggested to increase cortical excitability; however, rTMS with low-frequency trains decreases cortical excitability (Hallett, 2007; Di Pino *et al.*, 2014). High-frequency rTMS is associated to long-term depression and low-frequency rTMS to long-term potentiation (Muller *et al.*, 2014). TMS has been shown to increase motor-cortex excitability in acute stroke and improve motor outcome (Di Lazzaro *et al.*, 1999). An improvement of motor function in the hand contralateral to the stimulated hemisphere in chronic stroke patients was shown after transcranial direct current stimulation (tDCS) applied to the affected hemisphere (Hummel *et al.*, 2005). Although no neurophysiological measurements were performed, this improvement of upper limb function was assumed to depend on increased motor-cortex excitability in the affected hemisphere. It has been shown that rTMS over the affected hemisphere directly (recordings with epidural and myographic electrodes) increased motor-cortex excitability in the leg representation area and enhanced corticospinal output (Di Lazzaro *et al.*, 2006). Furthermore, a decrease in excitability in the unaffected hemisphere was observed (Di Lazzaro *et al.*, 2006). Despite the promising results, there is currently no clear evidence of the effectiveness of TMS in stroke rehabilitation.

Pharmacological manipulation

Antidepressants such as selective serotonin re-uptake inhibitors (SSRIs) are suggested to be potential and safe drugs to re-open the plastic window by changing cortical inhibitory circuits (Pariente *et al.*, 2001; Chollet *et al.*, 2011; Maya Vetencourt *et al.*, 2008; Yeo *et al.*, 2017). SSRIs treat anxiety and depression but may also ameliorate disability and neurological impairment after stroke although the results have been variable (Mead *et al.*, 2012).

Studies with rodents suggest that fluoxetine may enhance the plastic period by increasing the expression of brain-derived neurotrophic factor (BDNF) as shown in the visual cortex of rats (Maya Vetencourt *et al.*, 2008) and reducing the expression of inhibitory GABAergic inter-neurons in the spared cortex (Ng *et al.*, 2015). According to a meta-analysis, fluoxetine may improve gross motor function (Yeo *et al.*, 2017). Even a single dose of fluoxetine led to increased excitability in the affected hemisphere and improved performance in an active motor task in stroke patients (Pariente *et al.*, 2001). In a double-blind, placebo-controlled clinical trial, fluoxetine administration started within 5–10 days after stroke onset in conjunction with physiotherapy was shown to improve upper-limb motor recovery at three months (Chollet *et al.*, 2011). Another SSRI medication, paroxetin, has also shown, in addition of treating depression, to improve functional and cognitive performance after stroke and to mediate molecular mechanisms of neurorecovery (Chen and Zheng, 2014).

2.5 Magnetoencephalography

2.5.1 Overview

MEG is a noninvasive functional brain imaging method. MEG monitors electrical brain activity by measuring the associated weak magnetic fields outside the head. Since MEG has an excellent temporal resolution, it is well suited to study the dynamics of brain activity. The spatial resolution of a few millimeters, in favorable conditions, enables reliable localization of neural activity (Hämäläinen *et al.*, 1993).

The first measurements of the brain's magnetic field were performed in 1968 with a single-channel induction-coil magnetometer (Cohen, 1968). Some years later the sensitivity of MEG recordings improved profoundly with the invention of the SQUID (super-

conducting quantum interference device) magnetometer, which is employed in all commercial MEG systems today. At present, MEG systems comprise 200–300 channels and enable simultaneous recordings over the whole scalp and lend themselves to studying e.g. functional connectivity between cortical areas.

2.5.2 Neurophysiological basis

The MEG signals arise from synchronous electrical activity in tens of thousands of cortical pyramidal neurons; see Figure 2.1. Electrical signalling from neuron to neuron occurs through action potentials (AP), which are fired when the membrane depolarization at the axon hillock exceeds a certain threshold. An AP travels along an axon to reach synapses and trigger post-synaptic potentials (PSP). Synapses can be excitatory or inhibitory. If the sum of PSPs exceeds the threshold, it triggers an AP in this other neuron. The AP lasts only 1–3 ms and is associated with two opposite currents within the axon (Fig. 2.1d). This current pattern produces a quadrupolar magnetic field, which diminishes fast with distance. In contrast, PSPs are slower and they rather spread than propagate. Excitatory PSPs can last up to 30 ms and inhibitory ones even 80–100 ms (Hari and Puce, 2017). The PSP in the apical dendrite of a pyramidal neuron resembles a single current dipole producing a magnetic field that diminishes much slower than that of the AP. Thus, these PSPs produce most of the detectable magnetic fields. However, the intracellular currents are associated with return currents flowing in all surrounding conducting volume. These so called volume currents also produce a magnetic field, which may strengthen or weaken the field due to intracellular currents. Because of the effect of volume currents, MEG is most sensitive to activity in the walls of sulci where the apical dendrites are approximately tangential with respect to the head surface. (Hämäläinen *et al.*, 1993).

2.5.3 Instrumentation

The magnetic fields produced by neuronal populations are typically 100–500 fT at 2–3 cm above the scalp. These fields are orders of magnitude weaker than e.g. Earth's steady magnetic field (50–100 μT). The basis for MEG instrumentation is ultrasensitive superconductive magnetic field sensors, SQUIDs. To maintain superconductivity, SQUIDs are immersed in liquid helium.

In a typical MEG sensor, the neuromagnetic field is collected by a large pick-up coil,

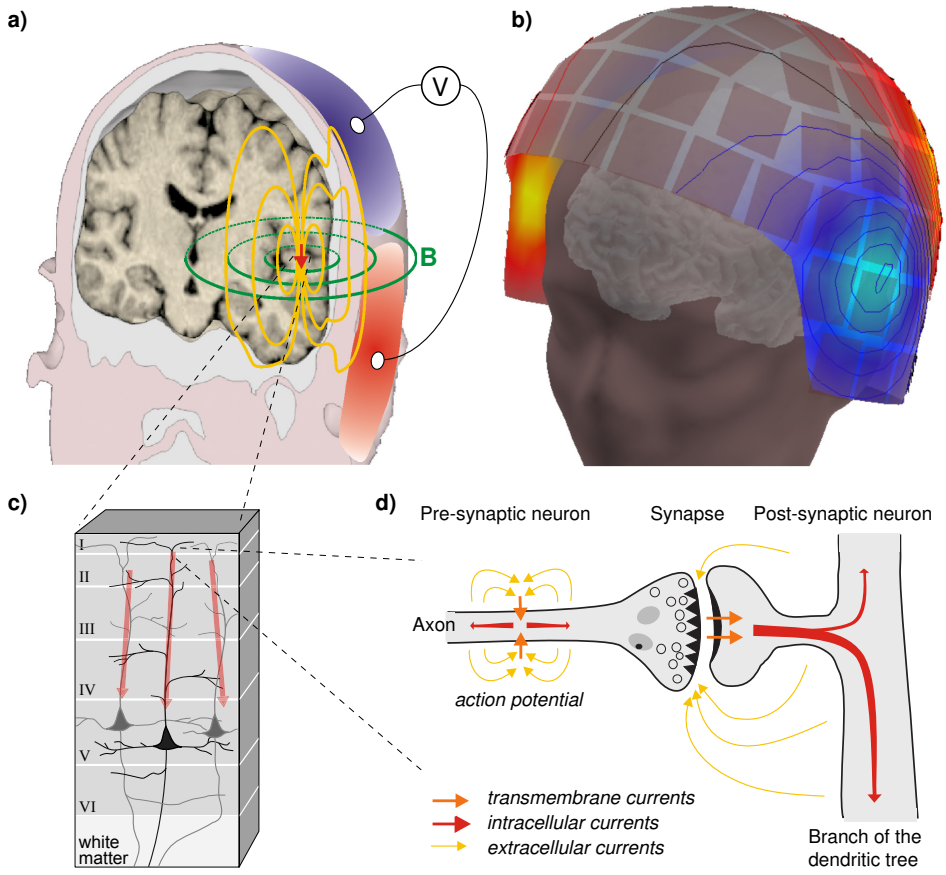

Figure 2.1 Generation of MEG and EEG signals. **a)** The magnetic field (B) and electric potential difference (V) produced by currents in an electrically active neuron population. **b)** MEG sensors measure the neuromagnetic field outside of the scalp. **c)** Post-synaptic currents in the apical dendrites of the Pyramidal neurons generate the fields measured with MEG and EEG. **d)** Intracellular currents are accompanied by extracellular currents flowing in the entire conducting medium. *Figure courtesy of L. Parkkonen.*

which induces a current in an input coil that is attached to a SQUID. Pick-up coils can be configured to measure different components of the magnetic field. A magnetometer is a single loop that measures the magnetic field perpendicular to the loop; while being very sensitive to neural sources, a magnetometer is also sensitive to interference. Gradiometers consist of two oppositely-wound loops and thus measure the difference of the field at the locations of the loops; a gradiometer is sensitive to nearby sources but effectively suppresses signals coming from the distance. The gradiometer loops can be in the same plane

(planar gradiometer) or along the common axis (axial gradiometer). Planar gradiometers output the maximum signal for sources right beneath them while axial gradiometers and magnetometers are most sensitive to sources some distance away from the pick-up loop. The MEG devices employed in this Thesis were designed and manufactured by Elekta Oy (Helsinki, Finland) and they comprise 306 channels (102 magnetometers and 204 planar gradiometers) in a helmet-shaped array.

The MEG measurements are performed in a magnetic shielded room to avoid environmental magnetic disturbances. The subjects are in a sitting or supine position with their scalp covered by the sensor array. The head position with respect to the sensor array can be measured continuously during the recording session. Yet, the subjects were instructed to keep their head still and try to avoid excessive blinking.

2.5.4 Source modelling

MEG sensor signals can be analysed directly (sensor-space analysis), which gives a coarse location of the underlying neural generators. By source modelling the signals, the sources can be localized more accurately. However, determining the sources of MEG and EEG signals is an ill-posed inverse problem, which does not have a unique solution. Yet, by applying physiologically plausible constraints, a unique source model can be estimated. An equivalent current dipole is often used in MEG to model a focal neuronal activation (Hämäläinen *et al.*, 1993).

In Study I, minimum-norm estimation (MNE; Hämäläinen *et al.*, 1993) was applied to localize neural generators. In MNE, one assumes that out of the various possible source-current distributions, the most likely solution has the smallest norm, i.e., the smallest total power. In this study, the temporal spectral evolution (TSE) method was applied to the result of MNE (Gramfort *et al.*, 2014, MNE Sofware), which enabled the localization of the sources of the 20-Hz rhythm modulation. The maximum rebound to tactile stimulation and passive movement of the index finger was estimated to be generated in the anterior part of the contralateral central sulcus, in the primary motor cortex.

2.5.5 Comparison of MEG and EEG

Both MEG and EEG signals originate from post-synaptic currents in cortical pyramidal cells. However, the orientation of the currents with respect to the head leads to a fundamental difference between EEG and MEG recordings. Signals detected by EEG are generated mostly by radial intracellular currents and to a lesser extent of tangential currents. However, radial intracellular currents are associated with volume currents that produce a cancelling magnetic field. Therefore, MEG signals are formed mainly from tangential currents, i.e., activations in the fissures.

Electrical potential distributions measured in EEG are distorted by different connectivities of tissues such as cerebrospinal fluid, brain, scalp and skull whereas magnetic fields remain unaltered between the cortex and sensors. This gives an advantage for MEG in source localization of cortical brain activity.

Both the EEG and MEG have an excellent temporal resolution of a millisecond.

3 Aims

The aim of this Thesis was to find a robust neurophysiological marker to monitor stroke-induced motor-cortex excitability changes. The dynamics of the 20-Hz rhythm, reflecting these excitability changes, was studied by using two different afferent inputs in healthy controls and in stroke patients in the acute, subacute and chronic phases after stroke. Thereafter, the motor-cortex excitability (the rebound strength) was correlated with functional recovery of the upper limb at these stages after stroke. This Thesis aims to offer an objective biomarker, which could be used during recovery from the acute to the chronic phase, especially in a severe stroke. The specific aims of the studies were as follows:

1. To evaluate, in healthy controls, how two different afferent inputs, tactile and proprioceptive stimulation, modulate the 20-Hz rhythm. The aim was to clarify the possible differential effects of these two stimuli on motor-cortex excitability.

2. To understand the role of altered proprioceptive input on motor-cortex excitability in both the affected and unaffected hemispheres in the acute phase, one and 12 months after stroke onset. Furthermore, the goal was to study how the observed changes in the excitability are associated with clinical recovery of hand motor performance.

3. To clarify how proprioceptive vs. tactile input affect motor-cortex excitability during recovery from stroke. The goal was to find out which of these two afferent input would better reflect the clinical recovery from stroke.

4 Materials and Methods

4.1 Subjects

4.1.1 Stroke patients

For Studies II and III, thirty patients (12 females, 18 males, age 45–78 years, mean 67 ± 2 years) with their first-ever stroke in the territory of the middle cerebral artery with unilateral upper limb paresis were initially recruited from the Department of Neurology, Helsinki University Hospital. The paresis of the upper, determined by the neurologist, varied from severe to mild but at least hand weakness or clumsiness were prerequisites for inclusion. Exclusion criteria were earlier neurological diseases, mental disorders, history of neurosurgery or unstable cardiovascular or general condition. Seven patients were excluded later during follow-up; two died, four declined the second or third MEG recording, and the data of one patient were contaminated with artifacts preventing reliable analyses. Eventually, 23 patients participated the study (10 females, 13 males, age 45–78 years, mean 65 ± 2 years). The Local Ethics Committee of the Helsinki and Uusimaa Hospital District approved our study protocol, and all subjects assigned written informed consent prior to the measurements.

4.1.2 Control subjects

The healthy subjects in Study I were used as the controls in Studies II and III. The control group comprised 22 volunteers (11 females, 11 males, age 42–72 years, mean 59 ± 2 years, all right-handed). All control subjects gave written informed consent.

4.2 Clinical evaluation

The patients underwent clinical examination in conjunction with the MEG recordings 1–7 days (T_0), 1 month (T_1), and 12 months (T_2) after stroke. Impairment caused by stroke was evaluated according to the National Institutes of Health Stroke Scale (NIHSS; 0–42). According to this scale, stroke impairment can be classified as mild (NIHSS < 8), moderate (NIHSS 8–16) and severe (NIHSS > 17). Independency in daily life was scored

with Barthel Index (BI; 0–100). BI and hand motor tests for the healthy and impaired hands were evaluated by the occupational therapists in HUH. Jamar Hydraulic Hand Dynamometer was used to measure the grip strength. Fine and gross manual dexterity was tested with Nine Hole Peg Board test (NHPT; time to remove and replace nine pegs into nine holes, maximum 180 s) and Box and Block test (BB; number of cubes moved from one compartment to another as quickly as possible in 60 s) tests, respectively. Proprioception was tested with a qualitative test in the impaired hand of the patients; the healthy hand was first positioned and the ability of the patient to mimic this position afterwards with the healthy hand was evaluated to be normal or abnormal.

Tactile sensitivity was evaluated with tactile detection thresholds by using Von Frey Filaments (3.22–3.61 normal or reduced light touch; 3.84–4.31 reduced protective sensation; 4.56–6.65 no protective sensation; 6.65 no measurable tactile sense).

4.3 Magnetic resonance imaging

In the patients, all anatomical magnetic resonance images (MRIs) were acquired in HUH 1-7 days (T_0) and one month (T_1) afters stroke with a 3 T MRI scanner (Philips Achieva 3T, Philips Medical Systems, Best, The Netherlands). For lesion size measurement at T_0, a diffusion-weighted sequence was used to detect ischemic lesions, and a T_2-weighted 3D-volume ($1 \times 1 \times 1 - \mathrm{mm}^3$ voxels) was acquired with the MRIcron software (McCausland Center for Brain Imaging, Columbia, SC, USA). The neuroradiologist of the research team classified the lesions as cortical when confined to the cortex and the immediate subcortical white matter without involvement of basal ganglia and/or capsula interna; subcortical if nucleus caudatus, putamen, globus pallidus, capsula interna and/or thalamus were involved; and cortico–subcortical if both cortical and subcortical areas were involved (Dromerick and Reding, 1995).

The anatomical 3D-T_1 MRI of one control subject for Study I to co-register the functional MEG results and the brain structure was acquired with a 3.0-T Signa VH/i (General Electric, Milwaukee, WI, USA) at the Aalto NeuroImaging, AMI Center, Aalto University, Finland.

4.4 Stimuli

4.4.1 Tactile stimulation

Tactile stimulation was used in Study I in healthy controls and in Study III in the patients. Tactile stimuli (duration 140 ms, peak at 50 ms) were delivered by using pneumatic diaphragms driven by compressed air (Mertens and Lütkenhöner, 2000) to the tips of both index fingers alternately with an interstimulus interval (ISI) of 1.5 s. (3 s. to one side) both to the patients and control subjects. To avoid perception of any stimulus-related sound the subjects wore earplugs.

4.4.2 Passive movement

Passive movement of the index finger was used as a proprioceptive stimuli in Studies I and II, and the data of passive movement from Study II was re-used in Study III. For passive movements, a laboratory nurse lifted briskly the subject's index finger with an ISI of about 3 s. To minimize tactile stimulation throughout the measurement, the index finger was covered with a surgical tape to which a rigid aluminum stick was attached for lifting the finger. To determine onset of the movement, two vertically placed optical gates with horizontally placed optical sensors in both were employed. The lower gate was located just above the finger at resting position and the upper gate was located 30 mm higher. The finger was lifted through the optical gates, and a stimulus trigger of the lower gate was accepted only if the finger passed first through the lower and thereafter the upper gate within 500 ms. About 60 accepted trials were collected.

To determine the passive-movement finger kinematics and the onset of the movement, a 3-axis accelometer (ADXL335 iMEMS accelerometer, Analog Devices Inc., Norwood, MA, USA) was attached on the nail of the index finger and its signals were acquired with the MEG system. As the passive movement actually started before the index finger reached the lower gate, the real onset of the movement was calculated off-line from the accelerometer signals in 17 controls and in 16 patients in Studies II and III. The accelerometer signals of 5 controls and 7 patients were lacking for technical reasons (the accelerometer signals were not available). The average lag (time from actual movement to recorded movement onset) was used for those subjects.

4.5 Magnetoencephalographic recordings

In both patients and controls, a 306-channel whole-scalp MEG system (VectorviewTM; Elekta Oy, Helsinki, Finland). The helmet-shaped sensor array, comprising 102 triple-sensor elements containing 102 magnetometers and 204 planar gradiometers, was employed for recordings. The measurements of 18 control subjects were performed in Aalto University and four controls and all the patients with similar measurement and stimuli devices in the magnetic-shielded room in the BioMag Laboratory (HUH, Finland). Prior to the recordings, four indicator coils as well as three anatomical landmarks (right and left preauricular points and nasion) and 50–100 additional points on the head surface were used for co-registration. During the recordings, the subjects were either in sitting or supine (four patients at T_0) position, and they were adviced to relax and to avoid excessive blinking. The subjects were instructed not to pay any attention to the finger lift or tactile stimulation. In addition, a sheet of paper was placed in front of the subject preventing her/him to see the passive movement. The subjects wore earplugs to avoid responses to stimulus-related acoustic noise.

The MEG and vertical electro-oculogram signals were pass-band filtered to 0.03–330 Hz and digitized at 1000 Hz. The nurse was present in the magnetic-shielded room to guide and observe the subjects and to perform manually the passive movements of the index fingers. During the 1.5-hour recording session, about 60 averaged trials were accepted for each hand for both the tactile stimulation and passive movement while acquiring continuous data for analysis. In addition, resting state data with eyes open and eyes closed (3 min each) were recorded. As control measurements in four control subljects in Study I, we used tactile stimulation with two different ISIs (1.5 s and 3 s) and two durations (140 ms and 1130 ms) to test possible effects of the different latencies and stimulus durations on the 20-Hz rebound.

4.6 Data analysis

4.6.1 Preprocessing

The raw MEG-data were pre-processed with temporal signal-space separation method (tSSS; Taulu and Simola, 2006), implemented in the MaxFilter^{TM} software (Elekta Oy, Helsinki, Finland). This method recognizes and removes both external interference and

internal artefactual signals from nearby sources (such as scalp and teeth).

4.6.2 Temporal spectral evolution

The modulation of the induced oscillatory activity (i.e. 20-Hz rhythm) was quantified with temporal spectral evolution method (TSE; Salmelin and Hari, 1994), which was used in all the studies. The dominant beta peaks were estimated from amplitude spectra computed from the resting-state data (eyes open), and the frequency band of the strongest modulation of the beta activity was determined by using time–frequency representations (TFR; Tallon-Baudry *et al.*, 1997). In the TSE computation, the preprocessed MEG data were filtered to the frequency band showing the strongest modulation (15–25 Hz in all subjects), rectified and averaged time-locked to the stimulus onset. We used analysis period of –100–1500 ms for responses to tactile stimulation and –100–2500 ms for passive-movement stimulation. The 100-ms prestimulus time was used to determine the individual baseline levels of rhythmic activity.

The stimulus-induced modulation, suppression and rebound, of the 20-Hz rhythm were then quantified from the TSE. The peak amplitudes of suppression and rebound over the rolandic area were quantified from one channel per hemisphere showing the strongest suppression/rebound of the 15–25-Hz activity both in the ipsi- and contralateral hemispheres to the stimulated hand. Thereafter, the relative peak amplitudes were calculated with respect to the individual prestimulus baselines and converted to percentages.

4.6.3 Spectral analysis

For estimating the peak frequencies of spontaneous oscillations, resting-state data were collected both eyes open and eyes closed. To evaluate the amplitudes of the oscillations, we applied fast Fourier transforms with a flat-top window of 2048 samples giving a frequency resolution of 0.5 Hz. The mu-rhythm frequencies were then quantified from the channels showing the strongest peaks.

4.6.4 Source modelling

Temporal spectral evolution was computed also in the source space in one control subject whose magnetic resonance image (MRI) was available to localize the sources of the

strongest rebound. FreeSurfer software (Fischl *et al.*, 1999) was used to segment the 3D head MRI of the subject for a single-compartment boundary element model and for the cortical mantle. Thereafter, cortically constrained L2 minimum-norm estimate was computed ("MNE Software"; Gramfort *et al.*, 2014). Noise covariance was estimated from a 2-min recording without a subject, filtered to 15–25 Hz. MatLab (Mathworks Inc.; Natick, MA, USA) functions were written for the TSE calculations in source space.

4.6.5 Statistical analyses

The Kolmogorov–Smirnov (KS) test was used to test for the normality of the data. In Study I of the healthy control subjects, the data were normally distributed but in Studies II and III with patients they were not. To make all variables normally distributed, we converted the original values x into new values $y = \ln(x+1)$ where $\ln(\cdot)$ is the natural logarithm. After this transformation, the KS test indicated normal distribution of all variables. These transformed variables were used in statistical analyses.

The kinematics of passive movements and clinical test results in the patients between the impaired and healthy hands were compared using a two-way (hands: impaired and healthy; times: T_0, T_1, T_2) repeated-measures ANOVA. The kinematics of passive movements were compared between the patients and the controls (values for right and left hands pooled) with one-way, six-level (2 x hand; 3 x time) ANOVA.

The TSE results from all sessions (T_0, T_1 and T_2) were studied in both the affected (AH) and unaffected hemispheres (UH) to both healthy- and impaired-hand tactile stimulation and passive movement. The variance within factors time, hemisphere and side of stimulation (contralateral/ipsilateral) was studied with a two-way within-subject ANOVA. Significant (threshold $p < 0.05$) main effects (F) were compared with paired-samples t-tests. Independent-samples t-tests were used when comparing statistically significant effects between controls and patients. Afterwards, Bonferroni correction (8 x) was used to compensate the effect of multiple comparisons. Spearman's parametric test was used in Study II and Pearson's non-parametric test in Study III for correlations analyses with thresholds $p < 0.05$.

5 Experiments

5.1 Study I: Modulation of the 20-Hz motor-cortex rhythm to passive movement and tactile stimulation

5.1.1 Motivation

Afferent input is shown to modulate motor-cortex excitability (Asanuma *et al.*, 1979; Abbruzzese *et al.*, 1981; Asanuma and Arissian, 1984; Favorov *et al.*, 1988; Cassim *et al.*, 2000, 2001; Gaetz and Cheyne, 2006; Houdayer *et al.*, 2006; Reyns *et al.*, 2008). Modulation of the 20-Hz rhythm appears as suppressions (event-related desynchronization, ERD in EEG) and subsequent rebounds (event-related synchronization, ERS in EEG) of the rhythm. During the movement or afferent input the rhythm is suppressed, reflecting activation of the motor cortex, whereas after cessation of the movement or afferent input, the observed rebound is associated to deactivation of the motor cortex (Pfurtscheller, 1981; Salmelin and Hari, 1994; Hari and Salmelin, 1997; Salenius *et al.*, 1997; Neuper and Pfurtscheller, 2001; Cassim *et al.*, 2000). In Study I, we compared how two different afferent input, tactile stimulation and passive movement of index finger, modulate the 20-Hz rhythm. The aim was to evaluate the effect of two somatosensory modalities on motor-cortex excitability and to use that information for monitoring motor-cortex excitability in stroke recovery.

5.1.2 Methods

The 20-Hz rhythm modulation to tactile stimulation was delivered by a pneumatic diaphragms to the tips of the index fingers alternately every 1.5 s to both sides (3 s in one side) and passive movement by manually lifting the index finger every 3 s (Figure 5.1). The afferent stimuli were delivered in conjunction with the MEG recordings. The environmental interference were eliminated with the temporal signal-space separation method (tSSS; Taulu and Simola, 2006). Amplitude spectra was estimated from the spontaneous data with eyes open to choose the channels with the strongest spectral peaks for Time-frequency representation in 0–40 Hz (TFR) method. TFR was used to find the band of strongest modulation in 20-Hz range. Thereafter, the strongest modulation of the 20-Hz rhythm was analyzed with a Temporal spectral evolution (TSE) of the planar gradiome-

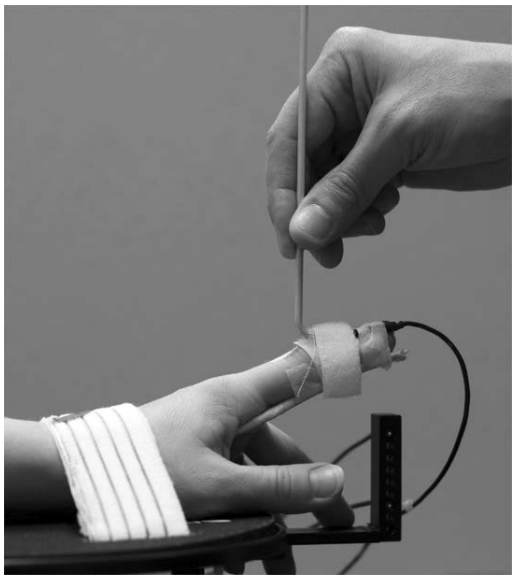

Figure 5.1 Setup for passive movement.

ters to quantify the modulation of the 20-Hz rhythm. The channels of the strongest suppressions and rebounds over the rolandic region in both left and right hemispheres were observed and quantified by using the baseline of -100 ms. The magnitudes of the 20-Hz rhythm modulation were calculated as relative values (%, peak amplitude/baseline), the peak latencies were also measured. In one subject, the source location of the rebound to tactile stimulation and passive movement was analyzed by computing the cortically constrained L2 minimum norm estimate from the TSE and the magnetic resonance image available (Figure 5.4).

5.1.3 Results

The peak latencies of the suppressions did not differ significantly between these two different stimuli or between hemispheres, whereas the peak latencies of the rebounds to passive movement were significantly ($p < 0.001$) longer than to tactile stimulation. The strongest modulation of the 20-Hz rhythm in TFR occurred between 15–25 Hz. The modulation of the 20-Hz rhythm was bilateral, but stronger in the contralateral hemisphere to the stimulated hand. Figures 5.2 and 5.3 show the modulation of the 20-Hz rhythm to

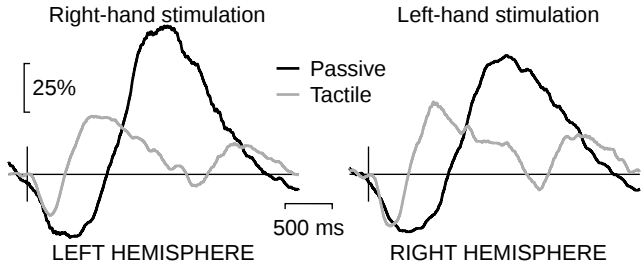

Figure 5.2 TSE of the 20-Hz rhythm in controls ($N = 22$). Grand average of the peak amplitudes of the 20-Hz rhythm, calculated as amplitudes relative to the pre-stimulus baseline (%), in the left and right hemispheres to contralateral tactile stimulation (gray) and passive movement (black) of right and left hand.

both stimuli: The suppression magnitude did not differ significantly between the hemispheres or between the two stimuli. However, passive movement induced a significantly stronger rebound than tactile stimulation in the contralateral hemisphere; to right-hand stimulation ($95 \pm 12\%$ vs. $60 \pm 8\%$; $p < 0.05$, respectively) and to left-hand stimulation ($89 \pm 14\%$ vs. $55 \pm 6\%$; $p < 0.01$, respectively). In addition, passive movement induced significantly stronger rebounds than tactile stimulation in the ipsilateral hemisphere; to right-hand stimulation ($48 \pm 6\%$ vs. $27 \pm 4\%$, $p < 0.001$, respectively) and to left-hand stimulation ($53 \pm 8\%$ vs. $28 \pm 3\%$, $p < 0.001$, respectively). In the MNE source location, the strongest 20-Hz TSE source was found anterior to the contralateral central sulcus (Figure 5.4).

5.1.4 Discussion

In Study I, in the healthy control subjects, passive movement induced a significantly stronger 20-Hz rebound than tactile stimulation both in the ipsi- and contralateral hemispheres. Thus, motor-cortex excitability is probably more potentially modulated by the proprioceptive than by tactile input. Therefore, passive movement could be used as a tool to monitor motor-cortical excitation/inhibition circuits in healthy population and in neurological disorders, such as in stroke. Since the suppression did not change between these two stimuli, the present study confirmed the previous findings that the underlying neuronal populations responsible for the activity during suppression and rebound are anatomically and functionally distinct (Salmelin *et al.*, 1995a,b; Pfurtscheller *et al.*, 1996; Jurkiewicz *et al.*, 2006).

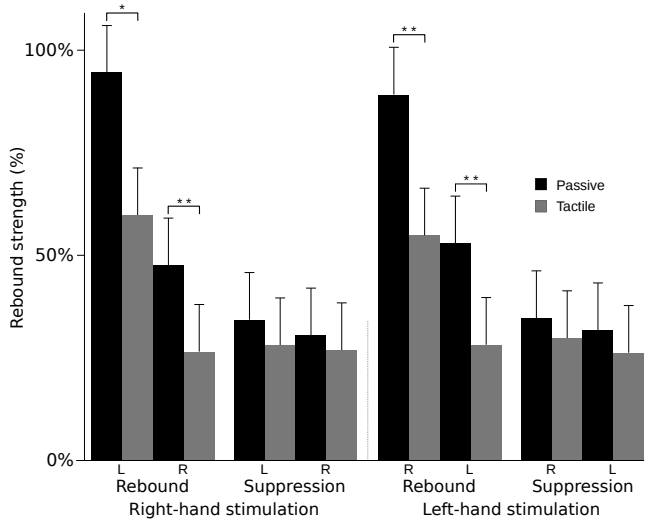

Figure 5.3 Strengths of the 20-Hz rebound and suppression relative to the baseline to right- and left-hand passive movement (black bars) and tactile stimulation (gray bars); $*p < 0.05; **p < 0.01$, L = left hemisphere, R = right hemisphere.

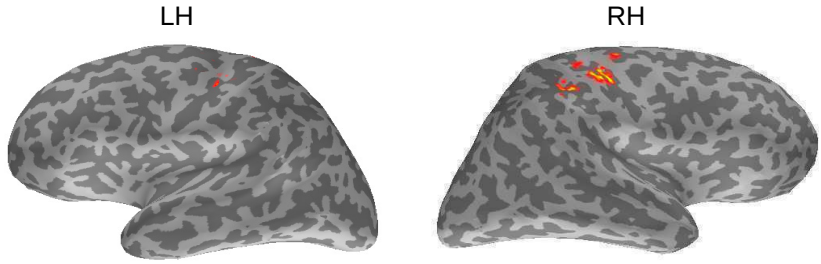

Figure 5.4 MNE-localization of cortical sources of the 20-Hz modulation to left-hand passive movement in one subject. The latency of the MNE maps correspond to the strongest rebound. The cortical surface views are independently thresholded at 60% of the maximum amplitude. LH = left hemisphere, RH = right hemisphere.

5.2 Study II: Strength of 20-Hz Rebound and Motor Recovery after stroke

5.2.1 Motivation

Stroke is a leading cause of disability in adults in the world (Donnan *et al.*, 2008; Lloyd-Jones *et al.*, 2009; Mozaffarian *et al.*, 2015). Several studies both in animals and humans have indicated that after a stroke there is a limited time (1 – 4 weeks) of plasticity; a sensitive period for restitution of lost neuronal functions by molecular, neurophysiological and structural changes (Nudo and Milliken, 1996; Biernaskie and Corbett, 2001; Biernaskie *et al.*, 2004; Barbay *et al.*, 2006; Wang *et al.*, 2011; Brown *et al.*, 2009; Murphy and Corbett, 2009; Jablonka *et al.*, 2010). Novel therapeutical methods, transcranial magnetic stimulation (TMS; Di Lazzaro *et al.*, 2006, 2012; Hummel *et al.*, 2005; Di Pino *et al.*, 2014; Wessel *et al.*, 2015; Hummel, 2017; Koch and Hummel, 2017) and antidepressants, serotonin reuptake inhibitors (SSRIs; Pariente *et al.*, 2001; Chollet *et al.*, 2011; Maya Vetencourt *et al.*, 2008; Chen and Zheng, 2014; Abramoff *et al.*, 2017) targeting to alter motor-cortical excitatory-inhibitory systems are suggested to enhance or even prolong plasticity. Still, more knowledge of the underlying neurophysiological mechanisms during stroke recovery are needed to evaluate the effectiveness and usefulness of these methods. The aim of this study was to better understand stroke-induced neuronal excitatory and inhibitory changes in both the affected and unaffected hemispheres from acute to chronic phases afters stroke by using passive movement as a proprioceptive stimulus.

5.2.2 Methods

MEG recordings were employed in 23 stroke patients (13 males, mean age 65 years; (Table 5.1) during a manual passive movement of the index fingers alternately in about every three seconds to the healthy and impaired hands. The MEG recordings were performed in an acute (T_0; 1–7 days), subacute (T_1; 1 month) and chronic (T_2; 12 months) phases after stroke. In conjunction with the MEG recordings recovery from stroke were estimated with NIHSS scale (National Institutes of Health Stroke Scale) and the hand clinical performance with Box- and Block- test (BB) and Nine-hole Pegboard test (NHPT). The proprioception was evaluated qualitatively by mimicking the position of the limb previewed. The anatomical magnetic resonance imaging (1.5 T, MRIs) were taken from each patient at T_0 and at T_1 to analyze the sites and sizes of the lesions. The analyzes used to quantify

Table 5.1 Clinical details of the patients.

			Lesion		
Patient	Gender	Age	Side	Site	Size (cm^3)
1	f	68	rh	c	1.78
2	f	59	lh	c	0.24
3	f	60	rh	cs	24.9
4	m	66	rh	cs	71.3
5	m	45	rh	cs	84.2
6	f	58	rh	cs	31.7
7	f	66	rh	cs	4.58
8	m	71	rh	cs	26.7
9	m	75	rh	cs	35.8
10	m	62	rh	cs	21.2
11	m	67	rh	cs	218.5
12	m	47	rh	cs	149.9
13	f	78	rh	cs	55.6
14	m	61	rh	cs	124.8
15	m	49	lh	cs	3.53
16	m	76	lh	cs	2.59
17	f	73	lh	cs	2.84
18	m	68	rh	s	1.36
19	f	59	rh	s	1.95
20	f	75	rh	s	13.0
21	m	64	lh	s	1.46
22	f	74	lh	s	40.0
23	m	74	lh	s	0.48

f = female, m = male, rh = right hemisphere, lh = left hemisphere, c = cortical, cs = cortico–subcortical, s = subcortical.

the data were same as in the previous study; TFR was used to find the strongest band of the 20-Hz rhythm and TSE to quantify the modulation of the rhythm to proprioceptive stimulation. Pearson's correlation analyze was used to calculate the correlation of the rebound strengths in the affected hemisphere to the impaired-hand (AH-impaired) and unaffected hemisphere to the healthy-hand (UH-healthy) passive movements with with the impaired- and healthy-hand clinical output (BB scores) of the patients at all time points from T_0 to T_2.

Table 5.2 Clinical scores of the patients.

Time	NHPT		Box-and-Block Test		NIHSS
	Impaired hand	Healthy hand	Impaired hand	Healthy hand	
T_0	104 ± 15**	27 ± 2	22 ± 5**	45 ± 3	6 ± 1
T_1	92 ± 16**	24 ± 1	32 ± 5**	54 ± 2	4 ± 1
T_2	82 ± 15**	24 ± 1	36 ± 5**	56 ± 2	2 ± 0

NHPT = 9-Hole-Peg Time (s); Box-and-Block Test = number of blocks moved; NIHSS = National Institutes of Health Stroke Scale (0–42); T_0 (1–7 days); T_1 (1 month); T_2 (12 months) after stroke. Scores of the impaired hand that differed significantly ($**p < 0.001$) from those of the healthy hand and are marked.

5.2.3 Results

MRIs revealed cortical strokes in two, subcortical strokes in six and cortico–subcortical strokes in 15 patients. The lesion sizes varied from $0.24 - 220$ cm^3 (mean 40 ± 12 cm^3).

Table 5.2 shows the clinical scores of the patients. NIHSS improved from T_0 to T_1 ($p < 0.001$) and from T_1 to T_2 ($p < 0.001$). BB scores for the impaired hand improved from T_0 to T_1 ($p < 0.001$) and from T_1 to T_2 ($p < 0.01$). The healthy-hand BB scores improved from T_0 to T_1 ($p < 0.001$) but not from T_1 to T_2. NHPT scores improved for the impaired and healthy hands from T_0 to T_1 ($p < 0.05$ and $p < 0.01$, respectively) but not from T_1 to T_2.

The modulation of the 20-Hz rhythm both in the affected and unaffected hemispheres to passive movement at T_0, T_1 and T_2 is shown in Figures 5.5 and 5.6. The rebound strength in the affected hemisphere to impaired-hand passive movement (AH-impaired) increased significantly from T_0 to T_1 and to T_2 ($p < 0.01$ and $p < 0.001$, respectively) but not from T_1 to T_2. The AH-impaired rebounds were significantly ($p < 0.001$) weaker compared to rebounds in the hemisphere contralateral to the stimulation of the control subjects ($N = 44$, hemispheres pooled) at all time points. Also the rebound strengths in the unaffected hemisphere to impaired-hand passive movement (UH-impaired) improved significantly from T_0 to T_1 and to T_2 ($p < 0.01$ and $p < 0.001$, respectively) and from T_1 to T_2 ($p < 0.01$). The UH-impaired rebounds were significantly weaker compared to the rebounds in the hemisphere ipsilateral to the stimulation of the controls ($N = 44$, hemispheres pooled); at T_0; $p < 0.001$, at T_1; $p < 0.01$ and at T_2; $p < 0.05$.

The rebound strength in the affected hemisphere to healthy-hand stimulation (AH-healthy) did not increase significantly during the one-year follow-up. However, the rebound strength was significantly weaker compared to that of the controls at T_0 ($p < 0.05$) but reached the level of the controls by T_1. The rebound in the unaffected hemisphere to healthy-hand passive movement (UH-healthy) increased significantly from T_0 to T_2 ($p < 0.01$) but not from T_0 to T_1 or from T_1 to T_2. The UH-healthy rebound was significantly weaker compared to that of the controls at all time points: at T_0; $p < 0.001$, at T_1 $p < 0.01$ and at T_2 $p < 0.05$.

Since only 15/23 patients could perform NHPT while 19/23 patients succeeded in obtaining above zero BB scores at T_2, the BB scores were used to correlate the rebound strengths with hand motor function (Figure 5.7). No correlations were found for the UH-healthy rebound strengths with healthy-hand clinical output. Significant correlations were found for the AH-impaired rebound strengths with BB scores of the impaired hand: At T_0; $r = 0.62$, $p < 0.01$; at T_1; $r = 0.73$, $p < 0.001$ and at T_2; $r = 0.57$, $p < 0.01$. No correlation was found between the lesion size and the rebound strength.

5.2.4 Discussion

The results of Study II showed that the rebound strengths of the 20-Hz rhythm to passive movement were significantly weaker in both hemispheres compared to those of the controls in the acute phase of stroke, reflecting bilateral hyperexcitability (disinhibition). The rebound amplitudes increased strongly during the first month of recovery, indicating a short plastic period after stroke onset. The rebounds did not reach the level of the controls (except in the affected hemisphere to healthy-hand stimulation). The findings indicate that stroke-induced motor-cortex hyperexcitability may be long-lasting. Furthermore, the rebound strengths of the affected hemisphere correlated with the impaired-hand clinical output: the stronger the rebound the better the hand motor performance. The correlation of the rebound strength in the affected hemisphere with the impaired-hand motor performance indicates that not only the motor-cortex excitability but also the afferent feedback from the impaired hand is affected by stroke, and that afferent input is of utmost importance for motor recovery. Furthermore, the rebound strength in the affected hemisphere in the acute phase correlated with hand-motor performance at one and 12 months, likely predicting motor recovery in the long run. Since the 20-Hz rebound amplitude of the affected hemisphere to passive movement reflects motor-cortical excitability–inhibitory balance, it could be used as a marker for evaluating and targeting therapeutic interventions aiming

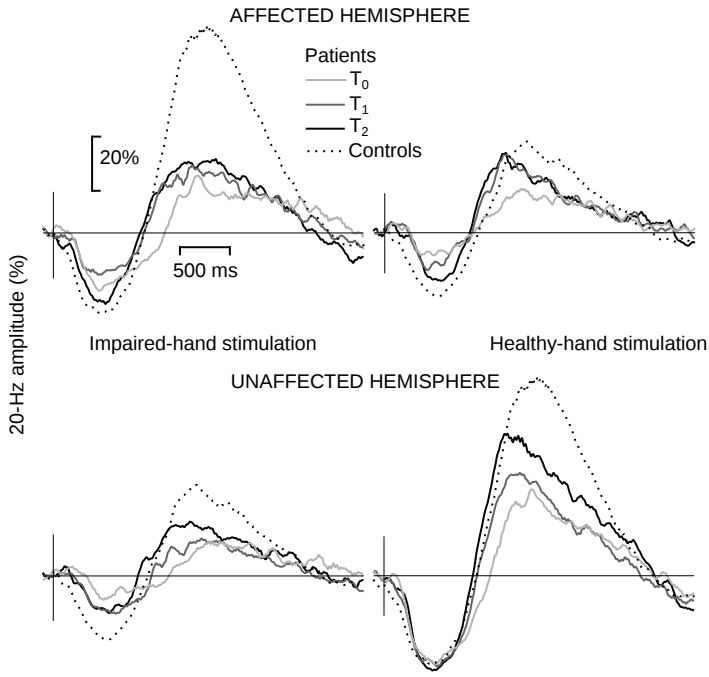

Figure 5.5 Alterations of the 20-Hz motor-cortex rhythm. Grand-average TSE of the modulation of the rhythm (amplitudes relative to baseline) in the affected (upper row) and unaffected (lower row) hemispheres to passive movements of the impaired- and healthy hands of the stroke patients ($N = 23$) compared to the contra- and ipsilateral responses of the controls (hemispheres pooled, $N = 44$). T_0 (1–7 days), T_1 (1 month), T_2 (12 months) after stroke.

to enhance plasticity.

5.3 Study III: Recovery of the 20-Hz rhythm to tactile and proprioceptive stimulation after stroke

5.3.1 Motivation

Stroke in the territory of the median cerebral artery often leads to upper limb paresis, in around 80% of all strokes (Lawrence *et al.*, 2001). Appropriate motor output is associated to intact sensation and proper integration of afferent input in the motor cortex. Afferent input is known to modulate motor-cortex excitability observable in the modulation of the

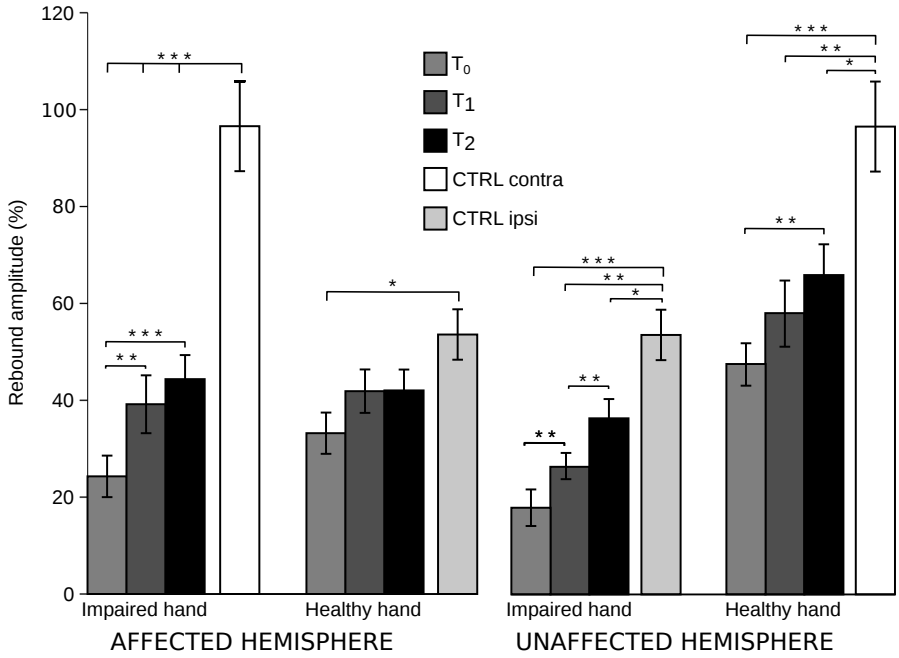

Figure 5.6 Comparison of the 20-Hz rebound strengths. Relative rebound amplitudes in the patients ($N = 23$) in the affected and unaffected hemispheres to the impaired- and healthy-hand passive movement compared to the contra- and ipsilateral responses of the controls ($N = 22$). CTRL contra (contralateral responses of the controls, hemispheres pooled; $N = 44$) and CTRL ipsi (ipsilateral responses of the controls, hemispheres pooled; $N = 44$). T_0 (1–7 days), T_1 (1 month), T_2 (12 months) after stroke; $*p < 0.05, **p < 0.01, ***p < 0.001$. Impaired hand (impaired-hand passive movement), healthy hand (healthy-hand passive movement).

20-Hz rhythm (Asanuma *et al.*, 1979; Asanuma and Arissian, 1984; Abbruzzese *et al.*, 1981; Favorov *et al.*, 1988; Cassim *et al.*, 2000, 2001). Study II and previous findings (Laaksonen *et al.*, 2012) have suggested that somatosensory integration to motor output is altered in stroke. In Study III, the aim was to compare the effect of two different afferent input, tactile and proprioceptive stimulation, on the 20-Hz rhythm of the patients during the one-year follow-up. In addition, the rebound strengths induced by both stimuli were correlated with hand motor function at all time points (T_0, T_1 and T_2).

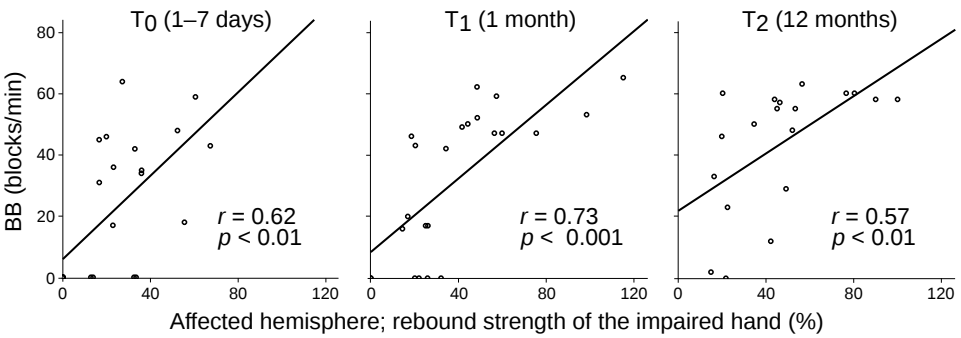

Figure 5.7 Correlation of the rebound strength with hand motor performance. Spearman's linear correlations of the relative rebound amplitudes of the affected hemisphere to passive movement of the impaired hand with Box-and-Block Test (BB) scores of the impaired hand.

5.3.2 Methods

The subjects (stroke patients and controls) and methods used in this study were the same as used in previous Studies I and II. For the first time, the modulation of the 20-Hz rhythm to tactile stimulation was studied in the patients during a one-year period. Here, we compared the rebound strengths in the affected hemisphere to tactile and proprioceptive stimuli of the impaired hand and those in the unaffected hemisphere to both stimuli of the healthy hand. The correlation between the rebound strengths to these two stimuli were calculated with Spearman's non-parametric test. We also tested the hand tactile sensitivity with Von Frey filaments.

5.3.3 Results

Table 5.3 shows the results of tactile sensitivity of the impaired and healthy hands of the patients in detail. Tactile sensitivity of the impaired hand was significantly ($p < 0.001$) worse than that of the healthy hand at T_0 and at T_1. Tactile sensitivity of the impaired hand improved from T_0 to T_1, but not from T_1 to T_2, and it remained significantly ($p < 0.05$) weaker than that of the healthy hand. Tactile sensitivity of the healthy hand improved significantly ($p < 0.05$) from T_0 to T_2, but not from T_0 to T_1 or from T_1 to T_2.

The modulation of the 20-Hz rhythm in the contralateral affected and unaffected hemispheres to tactile stimulation and passive movement during the follow-up is shown in

Table 5.3 Tactile sensitivity of the patients.

Time	Von Frey (mean ± sem)	
	Impaired hand	Healthy hand
T_0	4.56 ± 0.22**	3.74 ± 0.08
T_1	4.46 ± 0.23**	3.64 ± 0.06
T_2	4.33 ± 0.24*	3.57 ± 0.04

Von-Frey Filaments 1.65 – 6.65; T_0 = 1–7 days; T_1 = 1 month; T_2 = 12 months after stroke. The significance of the difference between the impaired and healthy hands: $^{*}p < 0.05$, $^{**}p < 0.01$,$^{***}p < 0.001$.

Figures 5.8 and 5.9. The suppression to tactile stimulation did not change significantly during follow-up. The AH- impaired rebound strength to tactile stimulation increased significantly from T_0 to T_1 and T_2 ($p < 0.001$) but not from T_1 to T_2. The UH-healthy rebound strength to tactile stimulation increased significantly ($p < 0.05$) from T_0 to T_1 but not from T_1 to T_2. The rebound strengths to passive movement are presented in previous Study II. Comparison of the rebound strengths between tactile stimulation and passive movement revealed that the rebounds to both stimuli behaved in a qualitatively similar manner throughout the follow-up period. The rebound amplitudes were significantly diminished in the acute phase both in the affected and unaffected hemispheres compared to the controls. The significant increase of the rebound amplitudes were observed during the first month after stroke to both stimuli. No significant improvement in the rebound strengths were observed from one month to 12 months. However, when compared to the controls, only the rebound amplitude to tactile stimulation reached the level of the controls by 12 months. The AH-impaired rebound to passive movement remained 46% and the UH-healthy rebound 67% of those of the controls at T_2 .

The rebound strengths both to tactile stimulation and passive movement correlated similarly and significantly with BB scores of the impaired hand (Fig 5.10): For tactile stimulation: at T_0; $r = 0.63$, $p < 0.001$; at T_1; $r = 0.68$, $p < 0.001$; at T_2; $r = 0.69$, $p < 0.001$ and for passive movement: at T_0; $r = 0.65$, $p < 0.001$, at T_1; $r = 0.78$, $p < 0.001$, at T_2; $r = 0.59$, $p < 0.01$. The correlations of the rebound strengths to tactile stimulation and passive movement with BB scores at T_0 and at T_2 were both significant ($r = 0.65$, $p < 0.001$ and $r = 0.57$, $p < 0.01$, respectively). Figure 5.11 shows that the rebound strength at T_0 predicts motor outcome (BB_2) at T_2. No correlations of the rebound

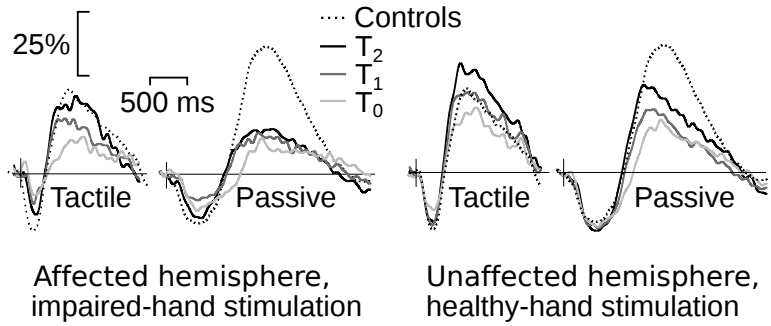

Figure 5.8 Modulation of the 20-Hz rhythm to two different stimuli during the follow-up. Grand average TSE of the modulation of the 20-Hz rhythm (relative amplitudes) of the patients ($N = 23$) in the affected hemisphere to impaired-hand tactile and passive stimuli and in the unaffected hemisphere to healthy-hand tactile and passive stimuli. The responses of the patients are compared to those of the controls ($N = 22$) to the same stimuli of the contra- and ipsilateral hands (hemispheres pooled; $N = 44$). T_0 (1–7 days), T_1 (1 month), T_2 (12 months) after stroke.

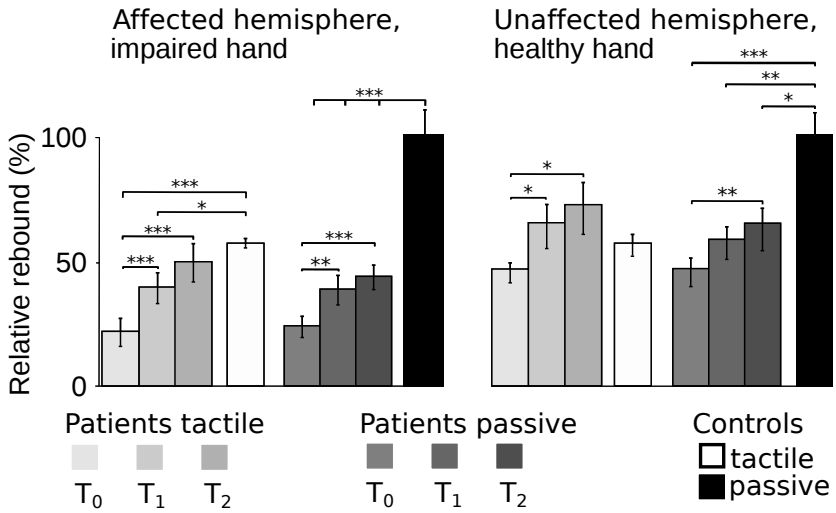

Figure 5.9 Changes of the 20-Hz rebound magnitude during the follow-up.The rebound strengths (%) in the affected hemisphere to both tactile stimulation and passive movement of the impaired hand and in the unaffected hemisphere to both stimuli of the healthy hand of the patients ($N = 23$). The responses of the patients are compared to those of the controls (hemispheres pooled; $N = 44$) to contra- and ipsilateral-hand stimuli. T_0 (1–7 days), T_1 (1 month), T_2 (12 months); $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

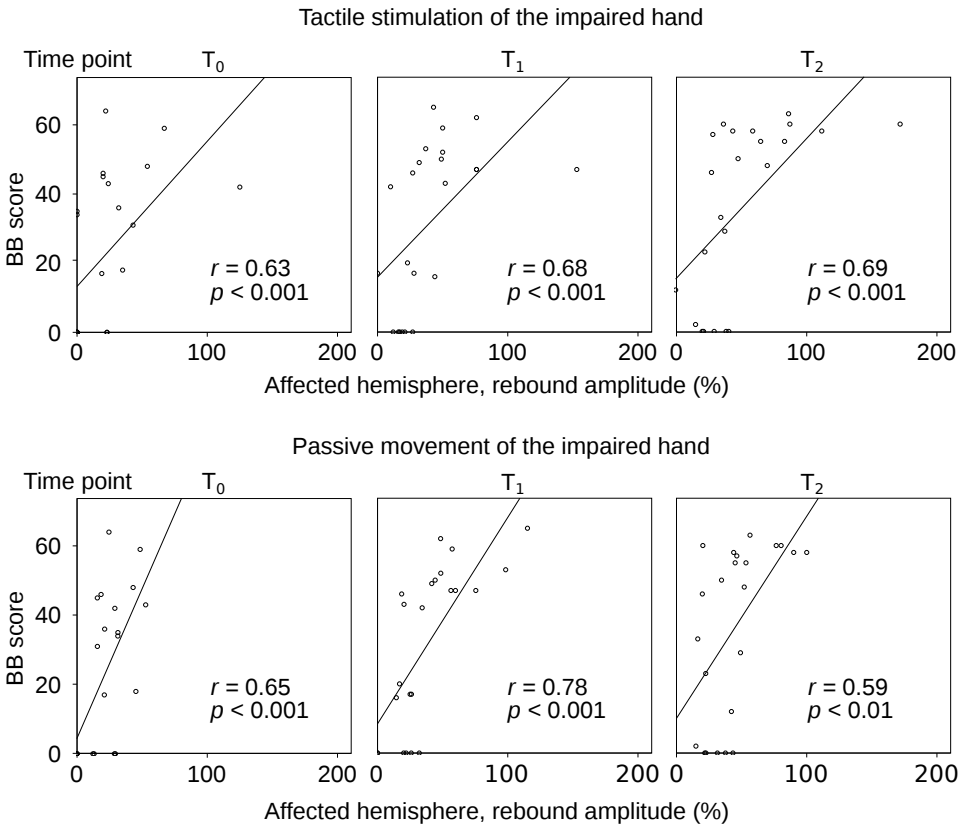

Figure 5.10 Correlation of the 20-Hz rebound amplitude with hand motor performance. Pearson's correlation of the 20-Hz rebound amplitude (%) of the affected hemisphere to tactile stimulation (upper row) and passive movement (lower row) of the impaired hand with Box-and-Block test (BB) scores across the follow-up. T_0 (1–7 days), T_1 (1 month), T_2 (12 months).

strengths to both stimuli with the lesion volume were found.

5.3.4 Discussion

The results in Study III indicate that both stimuli, tactile stimulation and passive movement, have similar temporal effects on the 20-Hz rhythm during the one-year follow-up. In accordance with Study II by using passive movement, the suppression did not change to tactile stimulation either. The rebound strengths within the patients were the weak-

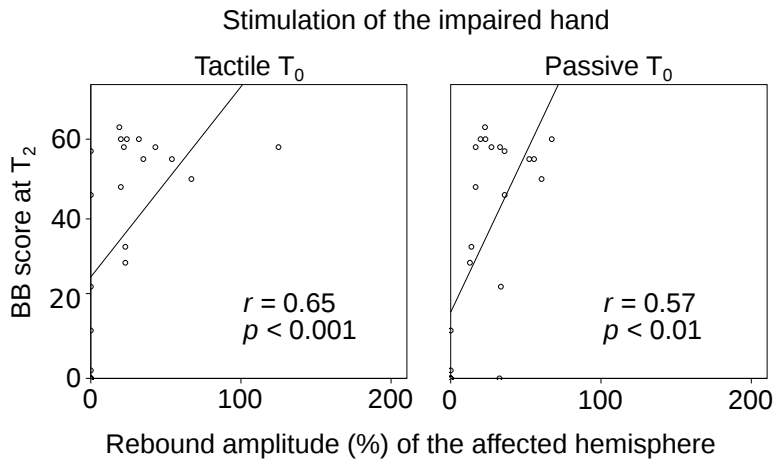

Figure 5.11 Prediction of motor outcome. Pearson's correlation of the 20-Hz rebound amplitude (%) at T_0 (1–7 days after stroke) in the affected hemisphere to tactile stimulation and passive movement of the impaired hand with Box-and Block test (BB) scores at T_2 (12 months).

est in the acute phase, similarly to both stimuli, and then increased strongly during the first month. The finding indicates that the sensitive plastic period, hyperexcitability or disinhibition of the motor-cortex, lasts only shortly after stroke, in line with the previous results in Study II. However, when compared to the rebound strengths of the controls, only rebounds to tactile stimulation recovered fully. The incomplete recovery of the rebound to passive movement may indicate that proprioception was not fully recovered in our patients. The possibility that the patients and the controls behaved differently during the MEG recordings (anticipation and planning of the forthcoming stimulation may have been stronger in the controls) cannot fully be excluded. Therefore, the factors affecting the rebound strength should be studied more in future to be able to make definitive conclusions from the results. Both tactile-stimulation and passive-movement induced changes in the 20-Hz rebound amplitude are equally suitable markers for studying stroke-induced neurophysiological changes. The correlations of the rebound strengths to both stimuli with hand motor performance were equally strong. The correlation of the the rebound amplitude in the acute phase with hand motor performance at one month and 12 months may predict recovery from stroke.

6 Discussion

6.1 General

In this Thesis, the modulation of the 20-Hz rhythm to afferent input was studied in healthy subjects and in first-ever stroke patients. The aim was to clarify how alterations in tactile sense and proprioception affect motor-cortex excitability and clinical recovery of hand functions. The goal was to find a robust neurophysiological marker for monitoring motor-cortex excitability during recovery; such an objective tool could be employed to evaluate and tailor rehabilitation. We also assessed if motor outcome could be predicted already in the acute phase of stroke.

6.2 Modulation of the 20-Hz rhythm to tactile stimulation and to passive movement

Our finding in Study I was that the 20-Hz rebound is stronger to passive movement than to tactile stimulation, indicating that proprioception could be more important for motor control than tactile sense. Furthermore, this result suggests that compared to tactile stimulation the passive-movement-induced rebound is more robust for studying alterations in motor-cortex excitability in healthy subjects and in patients in neurological conditions such as stroke. While the rebound strengths strongly depended on the type of afferent input, the suppressions did not. This dissociation adds further evidence that the suppression and rebound of the 20-Hz rhythm reflect activations of separate neuron populations, which is in line with earlier studies indicating that suppression and rebound have separate generation areas (Salmelin *et al.*, 1995a; Jurkiewicz *et al.*, 2006), slightly different frequencies (Pfurtscheller and Neuper, 1997; Pihko *et al.*, 2014) and distinct functions (Salmelin *et al.*, 1995b).

6.3 Stroke-induced changes in motor-cortex excitability

As described above, in healthy controls the rebound strengths to proprioceptive stimulation were stronger compared to those induced by tactile stimulation (Study I). However,

in Study III in stroke patients, the rebound strengths to both stimuli behaved in a similar manner throughout the one-year follow-up. Furthermore, the rebound amplitudes to tactile stimulation reached the level of the age-matched controls by one year after stroke but those to passive movement did not. This difference may indicate that – at least in our patients – stroke-induced deficits in proprioception are more profound than those in the tactile sense, which emphasizes the importance of focusing on proprioception in rehabilitation. However, the different strengths of the rebounds should be interpreted with caution since e.g. anticipation and planning of voluntary movements are known to increase cortical excitability and could thus result to stronger rebounds. Hence, subject-related factors, such as more pronounced anticipation of the passive movements in the controls, might have contributed to the higher rebounds.

The 20-Hz rebound amplitudes to both proprioceptive and tactile stimuli were the weakest in the acute phase but increased remarkably during the first month, concomitantly with the recovery of the affected hand motor functions. Studies II and III indicate that probably the first month after stroke represents a sensitive plastic period, thus being optimal for rehabilitation. In accordance with this, a previous MEG study showed that the rebound to tactile stimulation increased significantly from the acute phase to one month and no significant increase was detected between one and three months (Laaksonen *et al.*, 2012). However, the course of recovery may differ to some extent between patients.

Our results are in accordance with previous findings that rehabilitation during the sensitive plastic period in the acute phase after stroke associates with motor-cortex excitability changes in the spared surrounding sensorimotor cortex enabling reorganization of cortical ares and recovery of motor functions (Nudo and Milliken, 1996; Biernaskie and Corbett, 2001; Biernaskie *et al.*, 2004; Barbay *et al.*, 2006; Forss *et al.*, 2012; Kleim and Jones, 2008; Lohse *et al.*, 2014; Murphy and Corbett, 2009; Brown *et al.*, 2009; Wang *et al.*, 2011). Although the rebound seemed to recover up to 12 months, the changes between one and 12 months were not significant. However, some of the clinical scores of the patients did improve between one and 12 months indicating that even though the plastic window was closing some clinical improvement may still be achieved, likely via compensatory mechanisms. As rehabilitation was based on individual deficits and patients ability to participate in therapies was different, we cannot distinguish which part of the clinical improvement was due to recovery by learning or by compensation.

6.4 Sensorimotor integration and motor-cortex excitability

Afferent input conveys its effects on motor functions by modulating motor-cortex excitability, and appropriate feedback via afferent input is crucial for fluent motor performance (Abbruzzese *et al.*, 1981; Asanuma and Arissian, 1984; Favorov *et al.*, 1988; Cassim *et al.*, 2000, 2001). Accordingly, Study I in healthy subjects indicates that tactile and proprioceptive input strongly modulates the 20-Hz rhythm, observable especially in the changes of the 20-Hz rebound strength. However, afferent input and thus sensorimotor integration are impaired in stroke. Studies II and III in first-ever stroke patients indicate that in the acute phase after stroke sensorimotor integration was strongly impaired as the 20-Hz rebound to impaired-hand stimulation was the weakest in both the affected and unaffected hemispheres. During recovery from stroke, the rebound increased likely reflecting improved sensorimotor integration. Furthermore, the hand motor performance correlated strongly with the rebound strength during the follow-up period. The results throughout this Thesis indicate that afferent input and motor-cortex excitability are tightly interconnected, which strongly supports the notion that successful sensorimotor integration is crucial for motor recovery, again speaking for the importance of providing abundant afferent input in rehabilitation.

6.5 Plasticity-induced cortical reorganization

The early hyperexcitation of both hemispheres after stroke, observed in Studies II and III, likely reflects a sensitive stroke-induced plastic period. Plastic changes, associated to cortical hyperexcitability, enable formation of new intracortical networks (Swayne *et al.*, 2008) and restoration of motor functions (Liepert *et al.*, 2000; Bütefisch *et al.*, 2003, 2005). Several studies in animals with focal ischemic strokes have shown that recovery is associated with extensive reorganization of the motor cortex. In adult squirrel monkeys (Nudo and Milliken, 1996; Nudo *et al.*, 1996) and in rats (Jones and Schallert, 1992; Schiene *et al.*, 1999) cortical areas remote to the lesioned cortex have been demonstrated to undergo neurophysiological and structural changes indicating re-organization of the cortical areas during recovery. Importantly, rehabilitative training of squirrel monkeys enlarged sensorimotor areas (Xerri *et al.*, 1998) and the hand motor representation areas in the undamaged ipsilesional areas, whereas without training the motor performance did not improve (Nudo and Milliken, 1996). Patch-clamp recordings in mice have shown that disinhibitory changes in the peri-infarct zone were associated with enhanced plasticity.

However, the mice who performed forced rehabilitation recovered better than those who did not (Jaenisch *et al.*, 2016).

Similarly in humans, increased recovery-related disinhibition of the motor cortex during the acute phase of stroke is suggested to enable cortical reorganization (Bütefisch *et al.*, 2003; Ward *et al.*, 2003b,a). The following increased inhibition is suggested to allow motor recovery after stroke by recruitment of undamaged motor networks (Weiller *et al.*, 1992, 1993; Schiene *et al.*, 1999; Liepert *et al.*, 2000; Ward *et al.*, 2003b,a; Cramer and Crafton, 2006; Rehme *et al.*, 2012).

The results in this Thesis show that stroke induces changes in the 20-Hz rebound strength. These changes are likely influenced by alterations in gamma-aminobutyric acid (GABA) concentration or function since GABA-mediated inhibition is believed to play a key role in stroke-induced cortical excitability changes. In the acute phase after stroke the rebound strengths were the weakest indicating decreased GABAergic inhibition. However, animal studies have suggested that after the acute phase, increased GABA-mediated intracortical inhibition is a prerequisite for improved motor recovery (Calautti *et al.*, 2001; Schiene *et al.*, 1996; Jaenisch *et al.*, 2016). Congruently, Studies II and III showed that the rebound strengths increased during the first month and correlated strongly with the impaired-hand motor performance; the stronger the rebound the better the impaired-hand motor performance.

6.6 Recovery from stroke

According to the NIHSS scoring of our 23 patients, 16 of them suffered from mild and seven from moderate deficits in the acute phase. Only two patients reached 70% of their initial recovery potential as proposed by the proportional-recovery rule (Prabhakaran *et al.*, 2008). However, to assess upper-limb motor performance, we employed Nine-Hole Peg Board and Box-and-Block tests instead of the more comprehensive Fugl–Meyer scale typically used in the evaluation of proportional recovery, which may explain why the rule did not apply to our data.

None of the patients suffered from severe neurological deficits. However, NIHSS scoring may not be sufficient for evaluating hand dexterity – NIHSS might be zero although there is clear distal weakness or clumsiness of the hand. In five patients, the Box-and-Block test did not show any recovery of the hand motor function; the BB scores were zero even

12 months after stroke. No measurable rebounds were observed in these patients at T_0.

Correlation analysis showed that the stronger the rebound in the affected hemisphere at T_0 the better the hand motor performance at 12 months. Since most of our patients recovered poorly according to the applied clinical tests, we could not compare the neurophysiological features between the well and poorly recovered patients. However, motor-cortex excitability changes, reflected in the 20-Hz rebound, may offer a tool to study and predict the neurophysiological mechanisms underlying good vs. poor recovery in a larger group of stroke patients.

We found that lesion volume did not correlate with hand motor recovery, which suggests that the site of the lesion is a more important predictor of recovery than the size of the lesion. We tried to compare the patients according to the lesion site (cortical vs. cortico–subcortical vs. subcortical) but these subgroups were too small for drawing reliable conclusions.

6.7 Limitations and future recommendations

Since neuromagnetic fields remain largely unaltered between the cortex and the sensors – unlike electric potentials – MEG generally provides a better spatial resolution than EEG. However, MEG is an expensive technology and cannot be applied as a bed-side measurement. Thus, the feasibility of using EEG in quantifying the 20-Hz rebound should be studied.

The MEG recordings of our patients lasted about 1.5 hours, which was demanding to many of the patients especially in the acute phase and some patients could not remain continuously vigilant. Therefore, shorter measurement protocols should aimed at.

In this Study, passive movement was produced manually by an assistant. Although the same person performed the movements in all the patients and in 20 of the 22 controls, the stimulus might have varied slightly in terms of acceleration, amplitude and duration between the patients, controls and different sessions. However, it is unlikely that the observed changes in rebound amplitudes could be explained by the subtle changes in the passive-movement kinematics. Yet, MEG-compatible passive-movement actuators using computer-controlled pneumatic artificial muscles are recommended for future studies to ensure repeatability of the passive-movement stimulus.

The weaker recovery of the rebound to passive movement compared to tactile stimulation implies that proprioception did not recover as well as tactile sense did. However, this conclusion remains speculative as we could not precisely measure the recovery of proprioception in our patients because we used only qualitative clinical testing of proprioception.

Alertness and anticipation of a stimulus may affect the strength of the 20-Hz rebound. Some of the patients were drowsy during the recordings whereas the controls were generally alert and might thus have anticipated the passive movement resulting in stronger rebounds. Diminished muscle strength in the impaired hand of the patients may have reduced anticipation of the passive movement – resulting in weaker rebounds. Regardless, the significant increase of the rebound amplitude between the acute phase and one month was evident. The relationship between recovery of proprioception, muscle strength, and 20-Hz rebound strength should be explored in future studies.

6.8 Future approaches to boost recovery

Stroke rehabilitation should be more efficient in the future. Rehabilitation should take advantage of the limited post-stroke plastic period. Enrichment of the environment accompanied with properly-timed and intensive motor training are extremely important (Taub *et al.*, 1993; Liepert *et al.*, 2000; Biernaskie and Corbett, 2001).

Novel therapeutical methods, aiming at changing motor-cortex excitability, may augment and enhance plasticity. Transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) have been studied over ten years in the context of stroke rehabilitation. Yet, no clear success has been reached. It is known that the responses to TMS treatment are variable even in healthy persons. However, future studies building on the better understanding of the underlying neurophysiological mechanisms and related brain networks may offer more patient-tailored protocols and possibilities to augment plasticity (Di Pino *et al.*, 2014; Hummel, 2017; Koch and Hummel, 2017; Wessel *et al.*, 2015). Pharmacological manipulation with SSRI drugs, suchs as fluoxetine and paroxetine, may re-open the plastic window by changing cortical excitability (Pariente *et al.*, 2001; Chen and Zheng, 2014; Chollet *et al.*, 2011; Maya Vetencourt *et al.*, 2008; Yeo *et al.*, 2017).

There is an urgent need to evaluate these novel and possibly efficient therapeutical approaches. In this Thesis, MEG was used to study motor-cortex excitability changes af-

ter stroke. Since the 20-Hz rebound is a robust biomarker of motor-cortex excitability changes and motor recovery after stroke, it could be used to select the patients who would benefit from the therapies targeting to affect motor-cortex excitability. Rebound strength could be measured in the acute phase and at one and two months after stroke onset to see if the the rebound has continued to increase and whether the plastic window is still open. Hence, the 20-Hz rebound could be used to evaluate the efficacy of these methods before and after the treatment. This would help to develop properly timed and individually tailored methods in stroke rehabilitation.

7 Conclusions

This Thesis highlights the importance of afferent input in modulating motor-cortex excitability. In healthy controls, both tactile and proprioceptive input were found to modulate the 20-Hz motor-cortex rhythm by differentially affecting the rebound amplitude but not the suppression. Passive-movement induced 20-Hz rebounds were stronger than those to tactile stimulation, suggesting that proprioceptive input probably is a stronger modulator of motor-cortex excitability, and hence, likely more important in motor control.

The results in the patients corroborate the finding that stroke induces motor-cortical hyperexcitability in the acute phase, followed by increasing inhibition during the first month in both the ipsi- and contralesional hemispheres. In light of these results, the sensitive plastic period is suggested to occur only shortly after stroke, probably lasting only four weeks.

As stroke-induced disability leads to devastating individual suffering and economical burden for the society, novel therapeutical techniques targeting to enhance or prolong plasticity are in high demand. Since sensorimotor integration is tightly coupled with motor-cortex excitability, the afferent-input-dependent 20-Hz rebound magnitude could serve as a tool to evaluate the efficacy of new therapies already before and also after treatment and predict the patient's clinical outcome. Furthermore, the knowledge of motor-cortical excitability changes over time is important for tailoring an individual, appropriately-timed and maximally effective therapy and to avoid changing the excitatory–inhibitory balance in a harmful way.

This Thesis provides a robust neurophysiological marker to study stroke-induced alterations in motor-cortex excitability in different phases of stroke.

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